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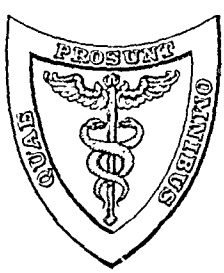
MEDICAL SCIENCES

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ORIGINAL ARTICLES.

SOME GENERAL FEATURES OF ENDOCRINE INFLUENCE ON METABOLISM.*

By W. B. Cannon, M.D.,

BOSTON.

(From the Department of Physiology, Harvard Medical School.)

A fairly constant or steady state, maintained in many aspects of the bodily economy even when they are beset by conditions tending to disturb them, is a most remarkable characteristic of the living organism. Though the blood is the common carrier for all manner of food material and for waste, its composition varies to a surprisingly slight degree. Though warm-blooded animals are exposed to numerous and extensive alterations of surrounding temperature, they themselves undergo shifts of temperature within only a brief range. And though food is taken in as it is provided or desired and is utilized as conditions may demand, the body weight of the full-grown individual continues for long periods on a strikingly even level. Since in these, and in other instances which could be added to them, circumstances are often present which, if not controlled, would profoundly modify the constancy of the state, we must assume that controlling factors are at hand ready to act whenever the constancy is imperilled. The existence of steady states in the body and some agencies maintaining them have, of course, long been recognized. On this occasion I am laying emphasis upon these states because of an interest in some

* Read as one of the papers in a symposium on Internal Secretion, Congress of American Physicians, Washington, May 6, 1925.

factors; on either side there may be two or more, brought into action at the same time or successively. Further, the two may be of different nature, for instance, an internal secretion and a neuromuscular agency.

A sixth proposition is that when a physiologic factor is known which can shift a steady state in one direction, it is reasonable to look for a physiologic factor or factors having a contrary or counterbalancing effect.

In the foregoing statements the expression "ready to act" has been used as an alternative to "acting" because in certain instances there is evidence that the situation is not kept balanced by direct and immediate opposition of active agencies, but is allowed to move to and fro within limits or within critical points, possibly under control of simple physicochemical adjustments, and only when these limits are passed are the more complex and indirect physiologic agencies (that is, those involving reactions peculiar to the organization of living beings) brought into play.

The advances in our knowledge of the relations of internal secretion to metabolism have lately been so great and so various that an attempt to present an encyclopedic survey in brief compass would be futile. Instead, may we not consider the six propositions, stated above, with regard to some recent investigations and results, and see to what degree interpretation is clarified thereby and new lines of work are indicated. In doing so I wish to disclaim any effort at an elaborate or final scheme of relationships. The concept of equilibrating factors will be used merely as a means of unifying some apparently diverse and separate observations which, in the main, have been personal experiences.

The Equilibrating Factors in the Blood-sugar Balance. Carbohydrate is the material most readily burned in the body. When it is provided in abundance the combustion of fat is almost completely stopped and the combustion of protein is reduced to a minimum. In less than half an hour after the ingestion of sugar the respiratory quotient usually rises to about 1.[4] The concurrent testimony of investigators supports the conclusion that carbohydrate is not only the most readily utilizable source of energy, but is essential for working the mechanism of muscular contraction. Its importance, therefore, need not be emphasized.

In the economics of the body, problems arise concerning carbohydrate demand and supply because that foodstuff is continuously being used up and is renewed only periodically. When it is taken in and is being digested it must not be permitted to increase in the blood above 170 or 180 mg. per 100 cc., for then it will be lost by escape through the kidneys. The amount available is likely to be more than is needed for current uses; the excess must be set aside in storage, in a compact and not immediately utilizable form. This is accomplished chiefly in the liver, though there are, of course,

and Rogoff, has found, not what they found, but what we found. Naturally Stewart and Rogoff[17] have criticized Kodama's results, and have declared that he did not master their technic. A recent letter from Sendai, however, states that other workers there have refined the method, and that Kodama's data have been fully substantiated. If any investigator anywhere had given Stewart and Rogoff any support for their contention that adrenal secretion is constant, and unaffected by conditions which induce sympathetic activity, there might be reason for seriously considering it. But that support is lacking. Opposed to it is the concordant experience of other investigators, derived from a variety of methods. It justifies confidence in the results obtained by use of the denervated heart as a signal for greater discharge from the adrenal medulla.

Now to return to the question of a sympathico-adrenal factor working to keep the blood sugar normal and to protect the organism from dangerous hypoglycemia. Among the hypoglycemic reactions which occur when an excessive dose of insulin has been given are pallor, a rapid pulse, dilatation of the pupils and profuse sweating. These are phenomena resulting from sympathetic impulses. The denervated heart tells whether the adrenal medulla shares in this increased activity. When, after an injection of insulin, the glycemic concentration is falling, it reaches a critical point at which the denervated heart begins to beat faster. And as the sugar percentage continues to fall the heart rate continues to rise until a maximum is reached. In the unanesthetized test animal the critical point lies between 70 and 80 mg. of glucose per 100 cc. of blood—a concentration at which in man also hypoglycemic symptoms first appear.[18] The faster beating of the denervated heart indicates that medulli-adrenal secretion has been stimulated. That inference is verified by removal of the glands, or by removal of one and denervation of the other, whereupon a fall of the glycemic percentage below the critical point is not accompanied by a more rapid heart beat. The faster beating of the heart, of course, indicates that impulses are being discharged along splanchnic fibers. These sympathetic impulses, in coöperation with increased adrenal secretion, might be expected to call forth sugar from the liver. This inference is confirmed by the fact that as the rate of the denervated heart increases (manifesting sympathico-adrenal activity), the rate of falling of the glycemic percentage is checked. And if not too much insulin has been given, the glycemic percentage may not only cease dropping, but may rise to normal. A highly significant feature of this sympathico-adrenal activity is that as the blood-sugar level rises the activity subsides. Indeed, when glucose is injected intravenously the activity has been seen to subside completely within two minutes.

Here is a remarkable mechanism having the function of keeping up the physiologic percentage of blood sugar when there is danger

of deficiency. After a dose of insulin the mechanism may be brought into service hours before a convulsion occurs, and if effective it may wholly protect against a convulsion. From the evidence provided by these observations we may conclude that the lower inner limit of variation of blood sugar, when the sugar is being withdrawn, lies in the region of 70 to 80 mg. Reduction below this limit calls into action a sympathico adrenal factor working to prevent further reduction. This factor works with increasing vigor the lower the glycemic percentage, until an acme is reached in a convulsion, when the denervated heart beats most rapidly.

According to Olmsted and Logan,[20] the convulsive seizures do not occur in a spinal animal, even when the glycemic percentage is extremely reduced. The sensitive region appears to be in the medulla or midbrain, for, in decerebrate animals typical convulsions result from hypoglycemia. Rapport and I[21] have shown that a center for medulli-adrenal secretion exists in the fore part of the floor of the fourth ventricle. Quite possibly this region is especially sensitive to a reduced sugar supply and by sympathico-adrenal discharges (culminating in spasms) protects the rest of the body against the hazards of too great a reduction.

Our results have received support from Abe,[22] who made use of the sensitized iris to signal a greater output from the adrenal medulla. In some instances he noted no effect, or very slight effect, during the first half-hour after giving insulin. Then there was a sudden change, marking the onset of the sympathico-adrenal function as the blood-sugar percentage fell. Houssay, Lewis and Molinelli[23] also have supported our conclusions. They employed a crossed circulation from the left adrenal vein of one dog to a jugular vein of another. When an insulin hypoglycemia was established in the donor, hyperglycemia was produced in the recipient—a result which did not occur if the left splanchnics of the donor had previously been severed. Both methods showed that adrenal secretion was increased by hypoglycemia, but unfortunately they were not used in such a way as to bring out the evidence for the critical point at which the sympathico-adrenal mechanism is set

administered to normal animals is capable of decreasing hepatic glycogen, that is, that insulin may work in the same direction with the sympathico-adrenal mechanism. There is excellent reason for believing, however, that insulin primarily is the opposing factor and that its apparently anomalous effect in normal animals should be regarded as a secondary phenomenon. Let us examine the basis for the inference that the internal secretion of the pancreas, or insulin, normally protects the body against hyperglycemia by promoting sugar storage in the liver:

1. There is the outstanding fact that removal of the pancreas is promptly followed by hyperglycemia and a great reduction in the hepatic glycogen reserve. This phenomenon is so well known as to need no emphasis.

2. As Banting and his collaborators[24] have shown, the administration of insulin to depancreatized animals not only brings the blood sugar down to the normal level, but causes glycogen to accumulate again in large amounts in the hepatic cells. Indeed, the hepatic glycogen of insulin-treated diabetic animals may be considerably more than in normal well-fed controls.

3. It has been found that insulin will induce a deposit of glycogen in the liver when the blood sugar is within the range of normal variations. Thus, Cori[25] has recently reported that the amount of hepatic glycogen may be quadrupled in phlorizinized rabbits by repeated doses of insulin.

4. Finally, as bearing on the antagonism between the glycogenolytic action of adrenin and the glycogenetic action of insulin, there may be cited the experiments of McCormick, Noble and O'Brien.[26] They discovered that when large doses of adrenalin were injected—doses which produced a marked reduction of hepatic glycogen in control animals—the additional injection of insulin was accompanied by a striking retention of the hepatic glycogen. The excessive doses of adrenalin used by them (for example, 2.5 cc. in a rabbit) allowed, they state, "enormous quantities of insulin" (for example, 140 units) to be tolerated without convulsions.

All these various observations bear witness to the importance of the internal secretion of the pancreas (insulin) as an agent operating conversely to the sympathico-adrenal mechanism in affecting the glycemic percentage by action on the liver.

The suggestion that insulin does not act in one direction only but in both directions on the liver (that is, glycogenetically and glycogenolytically) has, to be sure, been derived from experiments on normal animals. McCormick and Macleod[27] gave insulin and carbohydrates to rabbits rendered free of glycogen and found that less glycogen was deposited in the livers of the insulin-treated animals. Dudley and Marrian[28] compared the livers of glycogen-rich mice and rabbits, some of which had received insulin and others left as controls; the hepatic glycogen of the former was very

greatly reduced as compared with the latter. Babkin[29] also has reported that the glycogen content of the liver in well-nourished rabbits which had been given insulin is markedly lowered. The comments on these experiments have been somewhat equivocal. Thus Macleod[30] states that "There can be no doubt that insulin causes a rapid reduction in the amount of glycogen in the liver," but he also remarks later that at some stage after the blood sugar has become reduced by insulin, "The glycogenolytic process in the liver is stimulated." A similar suggestion was offered by Dudley and Marrian. In our third proposition we intimated that a factor does not have opposed functions with reference to the equilibrium which it protects. If we keep that idea in mind and remember that hypoglycemia calls forth sympathico-adrenal service, the results above detailed can be reasonably explained. It is significant that in the experiments of McCormick and Macleod, despite an effort to give doses of insulin "just insufficient to cause convulsions," convulsions occurred in 6 out of 15 cases; in the experiments of Dudley and Marrian the animals were killed on the appearance of convulsions; in the experiments of Babkin, though "convulsions were not observed," the glycemic percentage was far below the critical level. In all these experiments, therefore, the conditions were such that the hepatic glycogen stores were being drawn upon, not by direct action of insulin, but by the direct action of the factor opposed to insulin—the sympathico-adrenal factor—made to operate powerfully by the insulin hypoglycemia. This conclusion is supported by the testimony by Burn[31] that a small dose of insulin, mildly effective in the normal animal, causes in an animal treated with ergotamin profound hypoglycemia, with convulsions and collapse; for ergotamin, though having no influence on the action of insulin, paralyzes the protective sympathico-adrenal reaction. That the secreted adrenin plays an important part in this reaction is proved by the fact that the fall of the glycemic percentage is not checked, or is only slightly checked, at the critical point, if the adrenals have previously been inactivated,[5] and also under such conditions by the appearance of convulsions sooner and after smaller doses of insulin than in animals with active glands—a phenomenon observed by Sundberg,[32] by Lewis[33] and by us.[5]

From all the foregoing evidence it appears that the normal level of blood sugar is preserved by the sympathico-adrenal factor acting on the low side of the equilibrium and by the pancreatic factor and the renal overflow acting on the high side. Much still remains to be learned regarding the conditions bringing the islands of Langerhans into play. From the experiments of Banting and Gairns,[34] the inference may be drawn that a nervous control of insulin secretion is not necessary. That does not prove, however, that nervous control does not exist and could not be useful—the innervation of the heart is not *necessary!* The observations of De Corral[35] and of

McCormick, Macleod and O'Brien[36] point to vagus impulses as causing a discharge of insulin into the blood stream. Recent (unpublished) studies by Britton at the Harvard Physiological Laboratory, as well as the investigations of Clark,[37] have corroborated the earlier evidence. In harmony with these results are those announced by Lewis and Magenta,[38] that after section of the abdominal vagi a given dose of insulin is less effective than before. Because in the presence of high glycemic percentages remnants of the pancreas degenerate,[39] and the islet cells show signs of overwork,[40] it seems probable that just as the adrenals are stimulated by hypoglycemia, so likewise the "islands" are stimulated by hyperglycemia, that is, that each secretion is involved in a righting response which restores the normal equilibrium. If further research proves that the vagus provides a fine adjustment for insulin secretion, as the sympathetic does for adrenal secretion, it will be peculiarly interesting because of the common opposition between vagal and sympathetic functions.

A caution appears to be necessary here lest the ideas just expressed be taken as confirming Zuelzer's theory of the adrenal origin of diabetes. Indeed, Stewart[42] has declared that my interpretation of the sympathico-adrenal service in maintaining the normal glycemic concentration is only an elaboration of that theory. The essence of Zuelzer's theory was that the adrenals and the pancreas are such aggressive antagonists that when the pancreas is removed diabetes follows because of the unchecked action of the adrenals. The theory has no sound basis. And our observations, that sympathico-adrenal activity, roused by hypoglycemia, is promptly checked by hyperglycemia and that it is made to work again only when the blood sugar has *fallen* well below the usual level, should have prevented anybody from imagining that our experiments in any sense support Zuelzer's idea. Instead, they raise the question whether the high sugar level of diabetes may not be associated with a depression of sympathico-adrenal function.

It will be recalled that in our fifth proposition we suggested that when opposed factors assure an equilibrium there may be more than one on either side. Indeed, a primary action of the islands of Langerhans and the coöperative overflow arrangement in the kidneys may be regarded as a double device preventing a rise in the glycemic level. On the other arm of the balance may be placed the testimony of Olmsted and Logan,[20] that the pituitary body is important. They state that typical convulsive seizures occur in decerebrate animals if the pituitary body has been removed, but that otherwise even massive doses of insulin fail to lower blood sugar to a marked degree. This result has been associated with the observation by Burn,[31] that pituitrin can lessen or entirely prevent insulin hypoglycemia. The conclusion that the posterior lobe of the pituitary may collaborate with the adrenal medulla thus

seems justified. In a recent investigation, however, Bulatao and I[43] have shown that in decorticated animals with intact pituitary glands insulin regularly causes a drop in the glycemic concentration, and we have called attention to the same phenomenon in three similar cases described by Olmsted and Logan. Furthermore, we showed that in decorticated and decerebrated animals sympathico-adrenal activity may be maximal and may therefore retard or lessen the effect of insulin. For Olmsted and Logan to conclude on the basis of their few cases, which are not decisive, that the high blood sugar after decerebration is maintained by pituitary influence, seems to us unwarranted. In other words, though pituitrin as a pharmacodynamic agent inhibits the action of insulin, proof is still lacking that a pituitary secretion as such has that effect, and could coöperate with adrenal secretion.

Because of the effects which hypothyroidism, hyperthyroidism and thyroid feeding have in disturbing the glycogen content of the liver and influencing sugar tolerance,[44] and also because of reported hypersensitiveness of thyroidectomized animals to insulin,[45] it may be that the thyroid normally collaborates with the sympathico-adrenal apparatus. The evidence on this point is still too vague and uncertain, however, to justify discussion of it in this paper.

In our fourth proposition we mentioned that factors opposed in one region of the body may be collaborators in another region. This is perhaps the case with adrenin and insulin. They are opposed with respect to glycogen storage in the liver. They may be collaborators, however, in the utilization of sugar in muscles. Various investigators have found that injected adrenalin accelerates metabolism,[46] and recent Harvard studies have proved that secreted adrenin has the same effect,[47] and that the effect occurs when the circulation is almost wholly confined to muscles (not yet published). Adrenin causes in the isolated heart not only a greater consumption of oxygen per unit of time but also may cause total disappearance of the stored glycogen.[48] Hepburn and Latchford[49] observed that insulin accelerates removal of glucose from the perfusing fluid by the isolated mammalian heart, and Burn and Dale[50] noted that insulin causes rapid removal of glucose in a decapitated and eviscerated preparation, that is, when the heart and skeletal muscles are the only important metabolizing organs. The early stages of insulin action in such a preparation are characterized by increased oxygen consumption, with a respiratory quotient of unity. Thus insulin and adrenin, antagonists in the liver, appear to be collaborators elsewhere. Insulin may promote everywhere the passage of sugar from the blood into cells. In muscle cells adrenal secretion may work with insulin to facilitate the chemical changes underlying contraction. All this, however, remains to be proved. The suggestion is mentioned

here merely to illustrate the possibility of different relations of physiologic agents at different places in the organism.

Some Hints at Factors Affecting Protein Equilibria. Protein is quite as important as carbohydrate for bodily welfare and function. It is necessary for such invaluable services as building the cellular structure of the organism, repairing or restoring the worn or wasted parts, and providing the essentials for coagulation and for normal composition of the blood. It is constantly being disintegrated and lost from the body, and the possibility of securing a new supply is not always at hand. Since there is an elaborate arrangement for storing excess of carbohydrate and for liberating it as required, it would appear reasonable to look for a similar arrangement for storing indispensable protein against a time of need. The process of deaminization and the excretion of extra nitrogen indicate that accumulation of protein must be limited. The existence of a nitrogen equilibrium, capable of being altered and adapted to the requirements of the organism, implies that there prevails an orderly regulation for riddance or retention and the maintenance of a steady state.

The reality of a reserve or "deposit" protein has often been debated. Gradually there has developed a considerable body of evidence that with abundant protein feeding the hepatic cells can store protein just as they can store glycogen. More than forty years ago Afanassiew[51] noted that if "albuminates" were fed to dogs the liver became firm and resistant, and the hepatic cells increased in size and contained between their protoplasmic strands many fine sharply outlined granules, protein in nature. Seitz[52] brought further support, finding that in fed animals the total nitrogen of the liver in relation to that of the rest of the body was from two to three times as great as in fasting animals. The observations of Berg[53] have been especially significant. In 1914 he reported that in the hepatic cells of animals which are given protein there appear numerous small droplets or masses which are clearly distinguishable from the cell structure, which react as protein to Millon's reagent, which are caused to disappear by fasting, and which are restored only when protein or amino acids are fed. In 1922 he showed that these droplets can be distinguished in fresh teased-out liver cells stained with neutral red, and that they give the ninhydrin reaction of the simpler proteins. Berg's earlier observations have been fully confirmed by Stübel[54] and by Noel.[55] This histologic evidence for a protein reserve has been corroborated by Tichmeneff's chemical studies.[56] He starved mice for two days, then killed half of them and after giving the others an abundance of cooked meat killed them and compared the livers of the two groups. Expressed in percentage of body weight, the livers of the meat-fed animals had increased about 20 per cent, with the hepatic nitrogen content augmented between 53 and 78 per cent.

The concept of storage of valuable material involves the idea not of miserliness but of service—the appropriate use of the material outside the storage place. There appears to be at present no proof that protein is taken from the liver for use in another part of the body which requires restoration or improvement, though the possibility that such a transfer could occur would justify an attempt to search for it. There is testimony, however, to a function which the liver performs in maintaining the protein constituents of the blood. Kerr, Hurwitz and Whipple[57] found that after depletion of blood plasma (by bleedings and injections of washed blood corpuscles in Locke's solution) the restoration of the serum protein is delayed if the liver has been damaged or has been sidetracked by an Eck fistula. Furthermore, liver injury is associated with a fall in the serum proteins. Although in the blood of the normal animal fibrinogen is rapidly re-formed after being removed, Meek found that it fails to be re-formed if the liver is unable to act.[58] It seems, therefore, that the liver plays a fundamental role in the production of fibrinogen. In the production of antithrombin or antiprothrombin as well, and possibly of heparin also, there are indications that the liver is concerned and thereby might influence deeply the coagulation of the blood.

The serum proteins remain at a remarkably steady concentration, fluctuating only slightly with fasting, feeding, health or disease. And yet, as shown above, when they are reduced the liver soon restores them. Again the factors concerned with blood clotting are ordinarily in balance, so that coagulation takes a moderate and fairly uniform time. The relations can be disturbed, however, so that the time is longer or shorter. In experiments by Gray and myself[59] we obtained records of a shortening of the clotting time of blood by adrenalin injections if the blood is allowed to circulate through abdominal organs; the phenomenon fails if the circulation is confined above the diaphragm or if the intestines and liver have been removed. Increased adrenal secretion induced by splanchnic stimulation or excitement has a similar effect, as shown by experiments done in coöperation with Mendenhall.[60] According to Grabfield,[61] adrenalin increases the prothrombin element in the blood. It is significant that blood taken at the height of the hypoglycemic reaction, when sympathico-adrenal activity is maximal, "clots almost immediately it is withdrawn," as Macleod[30] has remarked, and as we also have noted. Finally, as Gray and Lunt[62] showed, a large hemorrhage hastens the coagulation of blood if the liver(and intestine) is in the circulation, but not if the blood flow is excluded from the abdomen. Since the sympathetic is stimulated by considerable hemorrhage, probably sympathico-adrenal action is normally involved in the response.

Additional evidence that the protein material of the liver can be called out by appropriate stimulation was furnished by Stübel,[54]

who found that the deposited droplets or small masses in the hepatic cells could be greatly reduced by injecting adrenalin subcutaneously. Moreover, in collaboration with Uridil and with Griffith,[63] we have shown that after protein feeding, stimulation of the nerves of the liver causes discharge of a still undetermined substance which accelerates the heart and causes a noteworthy increase of arterial pressure. The phenomenon is reduced to insignificance in animals which have been fasting, or which have been fed carbohydrate or fat.

From the foregoing observations we may conclude that the liver is an organ of central importance not only for carbohydrate, but also for protein metabolism. It shares with other parts the power of constructing protein from amino-acids, but when large amounts of protein are fed it lays by a reserve or deposit to a much greater degree than do the other parts.[56] This reserve can be called out by sympathetic stimulation and by adrenin. In maintaining the normal consistency and coagulability of the blood the liver is indispensable. Here are steady states in which the liver performs quite as important a task as it performs in the carbohydrate balance of the body, and probably the factors which control the situation act with quite as great a degree of nicety. Unfortunately we are still in a twilight zone which surrounds the problem, and vision is not clear. Hints have been given as to factors affecting the protein levels, but much work must still be done before we shall be well informed regarding them or their ways of producing steady states.

An Endocrine Factor Operating to Maintain the Temperature Equilibrium. The uniform temperature of warm-blooded animals, though they are exposed to very different environmental temperatures, has already been alluded to as an outstanding example of physiologic constancy. The temperature equilibrium is maintained by opposing factors. Concerning the nature of the physical factors, vasodilatation and sweating, which operate when the body temperature tends to rise, there has been no difference of opinion. On the other hand, factors which are set in action when the temperature tends to fall have been the subject of discussion for more than a third of a century. Speck,[64] Loewy,[65] Johansson[66] and Sjöström[67] have concluded from experiments in which subjects were exposed to cold surroundings that the increased metabolism which results is to be explained wholly in terms of shivering or other muscular contraction. Voit,[68] Rubner[69] and recently Leonard Hill and his co-workers,[70] on the contrary, have conducted experiments in which subjects were similarly exposed to cold surroundings, but usually for long periods, and have found acceleration of the metabolic rate with no demonstrable muscular movements. "It is incomprehensible," Rubner wrote, "that many physiologists can still doubt the presence of this powerful regulating mechanism. And it is just as

incomprehensible that the increase of heat in the presence of cold is ascribed solely to the gross shivering of the animal." What the nature of the chemical regulator is he did not suggest.

When warm-blooded animals are exposed to cold, the striking reactions are erection of hairs or ruffling of feathers, constriction of peripheral vessels and increase of blood sugar. These are signs that the sympathetic division of the autonomic system is in action. Is secretion from the adrenal medulla augmented under these conditions? The answer to this question has interesting bearings on the old controversy regarding chemical control of body temperature. Since 1906 various observers have found that adrenalin stimulates oxygen consumption in isolated organs or in the body as a whole. This pharmacologic evidence was given a physiologic significance when Aub, Forman and Bright,[71] at the Harvard Physiological Laboratory, found that if the adrenal glands are removed, though blood pressure and the body-temperature remain unchanged, the metabolic rate may drop as much as 25 per cent below the previous normal level, and when later McIver and Bright[47] demonstrated that increased adrenal secretion accelerates the oxidative processes of the body. Clearly, if cold excites a greater ourpouring of adrenin into the blood stream it would induce a faster burning in the body just when there would be need for it.

Cramer[72] and Fujii[73] have reported reduction of the chromaffin substance of the adrenal medulla in animals exposed to low temperatures, but that condition, as Trendelenburg[74] has suggested, may not have resulted from overdischarge but from underproduction. More direct evidence of an increased medulliadrenal secretion brought on by cooling was obtained by Hartman and his collaborators.[75] Using the completely denervated iris of the cat to signal greater discharge of adrenin, they observed that dilatation of the pupil resulted when the cats were dipped in cold water or when they were dipped in warm water, and while wet were placed in a cold room or exposed to a current of cool air. The dilatation failed to occur if the adrenal glands were removed or inactivated. The use of the iris by Hartman has been severely criticized by Stewart and Rogoff,[76] who, however, have not used the completely denervated structure themselves. They have, therefore, no good basis for judgment. Because Hartman's results have been doubted, and also because we desired to eliminate quite certainly any emotional element (which wetting may have roused in the cat), Querido and I[77] have investigated the reaction by other methods.

As in other experiments, we have employed the denervated heart as an indicator of augmented adrenal secretion. We tried several different modes of exposing animals to cold before we hit upon the one which proved most satisfactory—that of introducing into the stomach a known amount of ice-cold water. The body heat of the animal passes into the cold fluid, and, unless the temperature is

to fall, heat production must be increased to compensate for the loss. We have called the situation confronting the organism under the circumstances its "heat liability." Obviously, since the weight, the temperature and the specific heat of the water are known, the number of calories which the animal must conserve or produce, or both, in order to prevent a temperature fall, can be calculated and nicely adjusted to the purposes of the experiment.

When heat liabilities varying between 1050 and 2400 small calories per kilogram were established there were invariably faster rates of the denervated heart, ranging from 15 to 64 per cent increase. When the adrenal glands were inactivated, and similar heat liabilities were presented to the organism, the increases ranged between 2 and 6 per cent only. And if, instead of ice-cold water, water near the body temperature was used the percentage increase was negligible. Since cold slows the rate of the isolated heart, the faster rate which follows the introduction of cold water occurs in spite of adverse conditions, a true physiologic response. And since this response fails when the adrenal glands are not acting, the inference is justified that the faster heart rate is a consequence of greater adrenal secretion.

If the heat liability is more than 1000 calories per kilogram acceleration of the denervated heart is almost uniformly attended by shivering. Thus, two calorigenic factors, secreted adrenin and muscular movements, are coöperating to protect against a shift of the temperature equilibrium toward the low side. But the shivering factor is not an essential part of the reaction, for if a heat liability of only 900 calories per kilogram is to be met shivering rarely occurs; if it occurs it is of short duration. The heart rate is faster, however, showing that the adrenal factor is operating.

The increase of adrenal secretion when the organism is exposed to the danger of too rapid heat loss, and the ability of naturally secreted adrenin to accelerate heat production, point to a physiologic reaction the services of which to the organism ought to be demonstrable. To test the capacity of this reaction we have studied the effect of a certain heat liability on shivering when the adrenal glands were active or inactive, and we have observed the influence of heat liability on the metabolic rate in the absence of shivering.

I have already remarked that if a heat liability of 900 calories is presented to the organism (cat) shivering rarely occurs or is brief. In 15 cases shivering occurred only twice and lasted in each instance only three minutes. In 15 cases in which the adrenals were inactivated by removal of one gland and denervation of the other the same heat liability per kilogram caused shivering in 13, and furthermore the shivering usually lasted considerably longer than in the control series—for six, seven, eight, eleven, thirteen and even sixteen and seventeen minutes instead of three minutes.

Thus the primary protection against a heat deficit in the body is found in activities of the sympathetic system (erection of hairs, vasoconstriction, liberation of easily combustible sugar and discharge of adrenin), for these responses occur before shivering occurs and may be the only manifestation of the influence of a heat liability. If animals have been deprived of the calorigenic service of the adrenal medulla, however, greater demands are made on muscular activity as a means of maintaining the normal temperature. Under normal conditions, therefore, two lines of defense are erected against a shift of the temperature equilibrium toward the low side. The first line is the sympathico-adrenal mechanism; if that fails and the temperature tends to drop in spite of it, the second line, muscular action or shivering, is invoked to produce the needed heat. And just as the convulsive seizures in hypoglycemia are attended by a greater adrenal discharge, so likewise is shivering due to cold thus attended. In both circumstances the introduction of the muscular factors marks a climax of the action of the automatic arrangements for defense.

If the foregoing inferences are correct it should be possible to demonstrate a faster metabolic rate in response to a bodily need for heat, quite apart from any muscular quiverings or contractions. To secure evidence on this point Querido and I, and later Bright, Britton and I, have studied the change in the metabolic rate in human beings when a known heat liability was created by taking ice-cold water or that combined with ice. We have now 19 satisfactory observations on 12 different subjects. The heat liability ranged from 360 to 512 small calories per kilogram. The metabolic rate has increased in these cases as much as 35 per cent, though the usual increase was not more than 17 per cent, and this without any sign of shivering either objective or subjective. Commonly the first effect of taking the cold water is a drop in metabolism, which is followed by the rise, which reaches its maximum at

that a single factor, the muscular factor, is relied upon to keep the temperature balance from tipping downward. They bring support to the testimony and the argument of Voit and of Rubner, and offer an explanation of the chemical regulatory device which they postulated.

The evidence which has just been presented is not to be taken as excluding still other coöperating agencies. The fact that thyroid activity accelerates metabolism, that thyroid removal lowers the metabolic rate and renders one more sensitive to cold, that the thyroid gland is probably subject to sympathetic control,[78] that it enlarges in animals exposed to low temperature,[79] that in the compensatory hypertrophy of a remnant the evidences of hyperactivity are greater if the animal is exposed to frigid surroundings[80]—all these observations are highly significant of possible sympathico-thyroid collaboration in the upkeep of body temperature. As Aub[81] has suggested, the sympathico-adrenal service may be employed for quick action and the thyroid may act in the same direction, but for more enduring needs. But here we must have more facts before we are warranted in giving thyroid function definitely a place among the compensatory factors evoked by a threatened shift in the temperature equilibrium.

In the foregoing discussion I have used to a large extent the results obtained in personal investigations. This emphasis will not, I trust, be interpreted as implying an overvaluation of the subjects studied or of the results achieved. It seemed best to rely on first-hand experience rather than to summarize the work of others. Furthermore, I wished to illustrate the interest which is added to a search for new facts if certain general ideas are allowed to suggest the direction of the experimenter's imagination and his efforts at securing insight.

In stating the first of the six propositions, that is, that a steady condition in the body implies physiologic agencies serving to maintain it, I mentioned several types. The type of opposed agencies has been illustrated by the operation of the sympathico-adrenal and the probable vago-insular mechanisms in keeping normal the blood-sugar level, and also by the regulation of the temperature equilibrium by physical and endocrine factors. The outflow or escape type has been illustrated by the function of the kidneys when there is too great a rise in the glycemic percentage. Questions at once appear as to other constant metabolic states, such as the storage and disposal of nitrogen, the laying by of fat, and the constancy of the organic and mineral constituents of the blood. In all these equilibria what agents are at work to limit the variations? What types do they represent? Though there are hints of answers to these questions, reliable information must still be sought.

The second proposition, it will be recalled, postulated corrective activity whenever an equilibrium is disturbed. This service was rendered, as we have seen, by the sympathico-adrenal apparatus in the presence of both hypoglycemia and hypothermia. If this second proposition is generally true, not only must we look for agents which protect a steady state from serious disturbance, but also we must search for the control which makes them act with greater vigor, the more serious the disturbance. Related to this adjusted response is the fifth proposition: That accessory protective functions may be expected to coöperate if the primary functions fail. We have seen this situation in the coöperative activity of the kidney and the pancreas in resisting hyperglycemia, we have seen it also in the vasoconstriction, the increased adrenal secretion and the shivering which constitute progressively the three lines of defence against a drop in the temperature level of the body. We should keep our minds alert, therefore, not only for regulators of steady states but for the government of the regulators, and for the combination of regulators working toward the same end.

A general inquiry, important for clear understanding of body organization, would be one directed toward determining, so far as possible, the primary or immediate agencies, as contrasted with the secondary agencies, which induce a change of state. For example, we have seen that sympathico-adrenal stimulation is an immediate cause of glycogenolysis. Obviously any other condition inducing glycogenolysis may act, not directly on the liver, but through the sympathetic approach. Until the primary factors are known and properly recognized we are sure to have confusion—such confusion as is implied in the idea that a corrective agent operates in both directions at the same point.

In my opinion an attempt at present to develop an elaborate and intricate conception of the interrelations of the endocrine glands would be altogether premature and might be quite misleading. The necessary factors are not at hand. But the idea that endocrine factors play an important rôle in establishing and maintaining physiologic equilibria is reasonable and moderate in its scope, and does not involve a far-reaching projection of theory into the unknown. That the idea has value not only in raising questions regarding the existence and nature of balanced states but also in suggesting ways in which endocrine agencies may affect these states has, I hope, been made evident by the instances which I have cited.

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EFFECT OF ROENTGEN RAY IRRADIATION ON RED BLOOD CELL PRODUCTION IN CANCER AND LEUKEMIA.*

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Introduction. There are several views as to the nature of the action of Roentgen rays on living tissues. It is generally felt that small doses have a "stimulating" action, and that very large doses are "depressing." There is an intermediate dosage which frequently is noneffective in producing visible changes in living organisms. The "depressing" doses bring about their effects by causing the death of the tissue. Whether this destructive action is one of disturbed cell division, or whether it is corrosive, or whether it brings about its effects in some other way, is still a matter for investigation. Some light is thrown on this subject by observing the effects of Roentgen ray irradiation on the blood corpuscles of

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This paper is No. 60 of a series of studies on metabolism from the Harvard Medical School and allied hospitals. Expenses of this investigation have been defrayed, in part, by a grant from the Proctor Fund of the Harvard Medical School for the study of chronic diseases.

patients with leukemia or with cancer. The blood corpuscles offer especially suitable material for this investigation. The white blood cells may be recognized in the peripheral circulation from the myeloblast stage to the adult polymorphonuclear leukocytes. Of the red cells, the normoblast, the reticulocyte, the granule red cell and the adult red corpuscles may be recognized (Fig. 1). The granule red cells[1] are corpuscles which appear mature but contain, as their only differentiated internal structure, a refractive granule 0.5 micron in diameter. They represent a late stage in the maturation of the red corpuscle, and constitute about 1 per cent of the circulating red corpuscles in health. Changes in the percentage of reticulocytes and granule-red corpuscles can be observed during the course of a few hours after Roentgen ray therapy. The results can be interpreted numerically in terms of increased or decreased maturity. The effects of irradiation on the red blood corpuscles are found to be very definite when studied by this method.

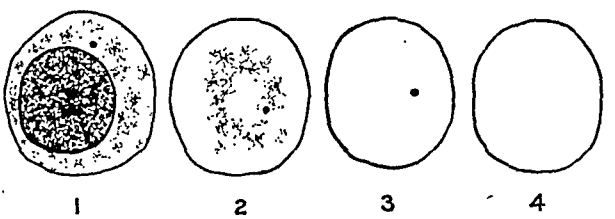


FIG. 1.—Four stages in the maturation of the red blood corpuscle, supravitally stained. (1) Normoblast; (2) reticulocyte; (3) granule red blood cell; (4) mature erythrocyte. The reticulocyte and the granule red blood cell are the two forms considered in studying the effects of irradiation in this paper.

Variations in Percentage of Young Red Blood Corpuscles. In order to evaluate the changes in the percentages of reticulated and granule red blood corpuscles after irradiation it is necessary to appreciate clearly the normal variations. In health, while the numbers of these corpuscles in the peripheral blood vary around 1 per cent, increases to 2 or 3 per cent may take place without evidence of disease. An increase above 3 per cent usually means an abnormal rate of blood production, and each degree of increase above this is of much more pathological significance than the variation below 3 per cent. The bone marrow appears to be "set" at a level of reticulated or granule corpuscle production with a physiological leaway of 1 to 3 per cent. Once the maximum is exceeded, small increments (1 per cent) are definitely significant. Thus a change from a total count of 1 per cent to a total count of 2 per cent has little pathological significance; whereas a change from a total count of 6 to 7 per cent has a much greater pathological import.

Previous Work on the Effect of Irradiation on Red Blood Corpuscles. Various observers have described changes in the number or the kind of red blood corpuscles after Roentgen ray or radium irradiation.

The data are not comparable because of the differences in dosage and technic.

Heineke[2] noted a late decrease in the number of erythrocytes after irradiation. Aubertin and Beaujard[3] described a decrease in the number of erythrocytes in irradiated rabbits with an increase in the young forms (polychromatophilia, blasts). Morris[4] found no changes in the number or cytology of the red blood corpuscles immediately after irradiation of animals. Weigeldt,[5] noticing the increase in the percentage of reticulocytes after irradiation, considered that the therapy had acted as an irritant to the bone marrow. Strumia[6] described the effect of radium placed over the extremities of a patient with myelogenous leukemia. He noted an increase in the number of nucleated red cells and other immature red blood corpuscles in the peripheral circulation during the week after the first application of radium, with a decrease after the subsequent treatments. The increase in the more immature forms during the initial period he considered as an evidence of bone-marrow stimulation. Millet and Mueller[7] recorded a considerable fluctuation of the number of red blood cells, with a definite increase in the count at some period within the first three days after irradiation of cases of squamous cell carcinoma of the cervix uteri and vagina with radium. Minot and Spurling[8] have reviewed the literature and from direct observations they conclude that there is no distinct or constant variation in the number or no specific change in the cytology of the red blood corpuscles during the course of days or weeks after therapeutic irradiation.

Material and Methods.—Blood for examination before and after Roentgen ray irradiation was obtained from 30 patients during the course of their clinical study. The cases included carcinoma of the breast, 6; of the uterus, 7; of the prostate, rectum, pancreas and stomach, 1 each; Hodgkin's disease, 2; chronic myelogenous leukemia, 7; chronic lymphatic leukemia, 1; erythremia, 2; chronic hemolytic jaundice, 1. Isolated observations were made on many other patients receiving Roentgen ray irradiation. Blood films were made on cover-glasses and stained supravitally with brilliant cresyl blue, with Wright's stain as a counterstain. Differential counts of 1000 to 5000 red blood corpuscles were made, representing from 30 to 150 or more microscope fields in different parts of the films. Hemoglobin determinations were made by the Sahli method. Wherever possible the blood was collected at the same time of the day and in the same relation to meals, and while the patients were at rest. The capillary blood from the ear was used. The total red blood corpuscle and leukocyte counts and the hemoglobin determinations were made by several persons, and must be interpreted with this in mind. All the reticulated and granule red cell counts were made by the author.

The irradiation was applied over the region of the neoplasm

or the spleen, lymph glands, or long bones. The number of electrostatic unit seconds and the area of exposure are given with each case discussed. The high voltage (170 kv.) constant potential short wave-length Roentgen ray described by Duane[9] was used. There was usually an average daily dose of about 600 electrostatic unit seconds (corresponding under these conditions to one-half erythema dose) exclusive of secondary irradiation, repeated on two to four successive days. The distance was 80 cm. in each exposure, and 0.5 cm. thickness of copper was used as a filter. The average effective wave length was from 0.170 A to 0.185 A degrees.

Data. The following are a few of the cases selected to illustrate the general principles shown by all the cases. Taking the changes in the percentage of granule red blood corpuscles as the criterion, the cases fall into three general groups. The first group comprises cases in which the granule red blood corpuscles increased in percentage during the Roentgen ray exposure, and remained above the preirradiation level for more than a day. A second group includes cases in which the increase in the percentage of granule red blood corpuscles was very transient, with a decrease to the pre-irradiation percentage or below by the following day. A third group is made up of those cases in which the rise in the percentage of granule red blood corpuscles was either absent or so transient that it was not detected, with an occasional decrease in the percentage below the pre-irradiation level.

TABLE I.—CARCINOMA OF THE BREAST.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)
1	....	2.5	5.9	89	0.75	9.8
2	....	2.2				
2	617 Portal 20 x 20 cm. Right breast, axilla, chest, anteriorly.					
3	....	4.3	4.7	92	0.97	11.0
4	....	4.0	4.5	94	1.00	8.0
5	....	3.2	4.8	96	1.00	7.8
7	....	2.4	5.6	....	....	9.6

Case Reports. CASE I.—*Carcinoma of the Breast.* A woman, aged fifty-one years. After a single exposure to the short wave-length Roentgen ray irradiation (Table I) there was both a relative and an absolute increase in the number of granule red cells, from 147,500 to 202,100 per cubic millimeter. The number gradually decreased and returned to the original percentage five days after the original treatment. There was a definite local improvement of the breast region clinically for four to six months. Later the processes became aggravated, and there was less response to treatment. Metastases appeared, and death followed in one year. No

leukopenia developed after this first irradiation. There was a slight decrease in the red blood cell count during the two days following the treatment, with a slight rise in the color index.

CASE II.—*Carcinoma of the Breast, Recurrent.* A woman, aged fifty-five years. The day following the first irradiation over the chest and mediastinum (Table II) the granule red cells had increased from 1 to 7.2 per cent, or an actual increase of from 60,000 to 388,800 per cubic millimeter. The next day the percentage had fallen to about its pre-irradiation level, and repeated treatments caused but a slight increase. The clinical results in this case were poor. It is not known whether leukopenia developed, as no further leukocyte counts were obtainable. There was a definite rise in the color index after irradiation, with a decrease in the red blood cell count.

TABLE II.—CARCINOMA OF THE BREAST.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)
1	600[1]	1.0	6.0	103	0.86	8.1
2	600[2]	7.2	5.4	110	1.02	9.2
3	500[1]	1.1	4.6	104	1.13	8.5
4	500[2]					
5	....	2.8	4.4	106	1.20	8.1
13	....	0.8	4.9	111	1.13	9.4

[1] Portal 20 x 20 cm. Chest, anteriorly. Given after blood counts were made.
[2] Portal 20 x 20 cm. Chest, posteriorly. Given after blood counts were made.

TABLE III.—CARCINOMA OF THE PROSTATE.

Day.	Roentgen ray, E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.
1	Before treatment[1]	2.6	2.2
1	500 portal 25 x 25 cm. Pelvis, posteriorly		
1	10 minutes after treatment	7.7	2.8
2	500 pelvis, anteriorly (after blood examination)	1.2	7.8
3	500 pelvis, posteriorly (before blood examination)	4.6	7.3

[1] Red blood cells, 2.7 millions per cu. mm.; hemoglobin, 60 per cent; leukocytes, 4700 per cu. mm.

CASE III.—*Carcinoma of the Prostate.* A man, aged seventy-five years. In contrast to the preceding individual, this patient had a marked anemia. There was a rapid increase in the percentage of granule red cells (Table III) noted ten minutes after the initial exposure, and a decrease in the percentage of reticulocytes. With the subsequent decrease in the percentage of granule red cells on

the following day, the percentage of reticulocytes increased and was sustained after subsequent treatments. The clinical results in this case were poor. A leukopenia was present in this patient before irradiation.

CASE IV.—*Carcinoma of the Rectum.* A man, aged sixty years. As shown in Table IV, irradiation was followed by very slight changes in the number of granule or reticulated red blood cells. There was a fair but temporary improvement in the rectal condition.

TABLE IV.—CARCINOMA OF THE RECTUM.

Day.	Roentgen ray, E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.
1	.....	2.0	0.2[1]
2	.....	2.3	0.5
2	500 pelvis, posteriorly portal 20 x 20 cm.		
2	1 hour later	0.9	0.3
2	4 hours later	2.6	1.2
3	500 pelvis anteriorly portal 25 x 25 cm.[2]		
3	First 30 minutes of exposure	0.8	1.4
3	2 minutes after total exposure	0.9	0.6
3	4.5 hours after treatment	0.9	0.7
4	500 pelvis, posteriorly portal 25 x 25 cm.		
4	1 hour after	1.4	1.3

[1] Leukocytes, 11,400 per cu. mm.; hemoglobin, 75 per cent.
[2] Red blood corpuscles 5.73 millions per cu. mm.; hemoglobin 93 per cent; leukocytes, 15,000 per cu. mm.

TABLE V.—CARCINOMA OF THE STOMACH.

Day.	Roentgen ray E.S.U. Sec.	Granule red blood cells, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands per cu. mm.)
1	....	1.5	4.3	68	0.79	20.0
1	500[1]					
2	....	0.6	4.4	77	0.86	21.0
2	500[1]					
4	....	2.1	3.8	68	0.89	17.0
22	....	0.6	5.2	77	0.74	15.0

[1] Portal 20 x 20 cm. Epigastrium.

CASE V.—*Carcinoma of the Stomach.* A man, aged fifty-six years. On the day following the first treatment (Table V) the relative and actual number of granule red cells decreased, without significant change after a second treatment. These changes were within the limits of normal variations. The color index rose very slightly after the treatment with a decrease in the red blood cell count. Eighteen days later the red cell count had risen with a

differential leukocyte count, and very little change in the percentage of granule red blood cells. After two erythema doses of short wave-length Roentgen ray irradiation there was a marked change both clinically and in the blood. The increase in percentage in granule red cells was from 1.1 per cent before the irradiation to 6.3 per cent after it. This preceded the changes in the white blood cell count by twenty days. The difference in the action of the Roentgen rays and radium was probably a matter of dosage and not the result of any intrinsic differences of the two sources of radiation.

TABLE VIII.—HEMORRHAGE. CARCINOMA OF THE CERVIX OF UTERUS.

Day.	Roentgen ray, E.S.U. Sec.	Granule red blood cells, per cent.	Reticulocytes, per cent.	Red blood cells (millions per cu. mm.)	Hemoglobin, per cent.	Color index.	Leukocytes (thousands, per cu. mm.)
1	Hemorrhage[1]						
3	.....	5.0	3.3	3.6	55	0.76	10.0
4	.....	4.6	4.5				
5	.....	4.3	5.9				
6	.....	2.2	6.3				
7	.....	6.4	5.6				
8	.....	4.0	5.6				
9	.....	2.2	5.3	2.7	55	1.02	10.9
9	600[2]						
10	.....	1.6	5.2	3.4	55	0.81	11.0
10	600[3]						
11	.....	7.0	5.4				
11	500[2]						
12	.....	8.0	4.1	3.1			
12	500[3]						
12	10 min. after roentgen-ray	8.8	4.5				
13	.....	8.9	4.1				
14	.....	6.6	4.6	3.6	55	0.76	

[1] Severe hemorrhage from cervix of uterus for eight hours.
[2] Portal 20 x 20 cm. Pelvis posteriorly.
[3] Portal 25 x 25 cm. Pelvis anteriorly.

CASE IX.—*Hodgkin's Disease.*—A woman, aged twenty years. Short wave-length Roentgen ray irradiation failed to produce an appreciable change in the percentage of young cells during a period in which two transfusions failed to stimulate an increase in their number. During another period a transfusion was successful in increasing the number of granule red cells and an irradiation at this time had a similar effect. Two days after this irradiation the granule red cells decreased from 6.4 to 2.8 per cent, with a rise during this period in the percentage of reticulocytes, from 1.9 to 3.8 per cent. Before the irradiation the color index was 75 and the day after it was 103.

CASE X.—*Erythremia.* A woman, aged forty-four years. During the course of twenty-four hours after an erythema dose of short wave-length Roentgen ray irradiation over the long bones there was a slight but definite increase (from 3.3 to 4.5) in the number and percentage of the granule red cells. Six days later the percentage had decreased below the pre-irradiation number (1.9 per cent), and the percentage of reticulocytes had increased considerably (from 2.2 to 6.9 per cent). The color index before irradiation was 0.62. On the day after the treatment it was 0.72, and six days later it had risen to 1. In another case (male, aged forty years) there was an increase from 1.6 to 3.3 per cent in the number of granule red cells immediately after one short wave-length Roentgen ray irradiation treatment over the splenic region.

CASE XI.—*Carcinoma of the Cervix of the Uterus with Hemorrhage.* A woman, aged forty-eight years. After a severe hemorrhage from the cervix, the percentage of granule red cells was increased above normal (Table VIII), followed later by an increase in the percentage of reticulocytes. With the second Roentgen ray exposure the number of granule red cells increased from 1.6 to 7 per cent, reaching 8.9 per cent after the fourth treatment. It will be noted that while the percentage of granule red cells rose, the percentage of reticulocytes still remained above normal.

Discussion. The data from the preceding cases as well as those from the other cases studied, but not reported in this paper, were essentially similar. No gross differences in effects of Roentgen ray irradiation on the red blood corpuscles were associated with age (there were no young children in this series) or with sex. A single instance of a relation of temperature and granule red cell number was encountered in a case of chronic myelogenous leukemia, in which both the temperature (102° F.) and the granule red cell count which had been elevated for six days (3.1 to 5.1 per cent) suddenly fell to normal and remained so. The actual number of red blood corpuscles per cubic millimeter was not affected in as definite a manner as the number of leukocytes in any of the patients. The study of the cases, both those reported in the tables and others, shows that they may be divided into three groups on the basis of the changes in the numbers of granule red blood cells after irradiation. The first group includes those in which there was, after irradiation, an appreciable increase in the number and percentage of granule red blood cells which did not decrease to pre-irradiation level for a period longer than twenty-four hours (Cases I, VI, VIII and XI). The second group is made up of those in which the increase in the number and percentage of the granule red blood cells was present less than twenty-four hours before dropping to the pre-irradiation level (Cases II, VII and X). The third

group includes those in which the increase, if present at all, was so transient that under practical conditions it would be overlooked if the blood were not examined soon enough after irradiation was begun (Cases IV, V and IX). In some of the third group of cases no change may have taken place in the granule red cells at any time (Fig. 2). When classified according to the clinical course the cases fell into the same groups. In those patients in whom the rise of granules red blood corpuscles lasted at least two or more days the clinical results were good. In those cases in which no definite increase in the granule red blood corpuscles was noted after irradiation there was usually no clinical improvement in the irradi-

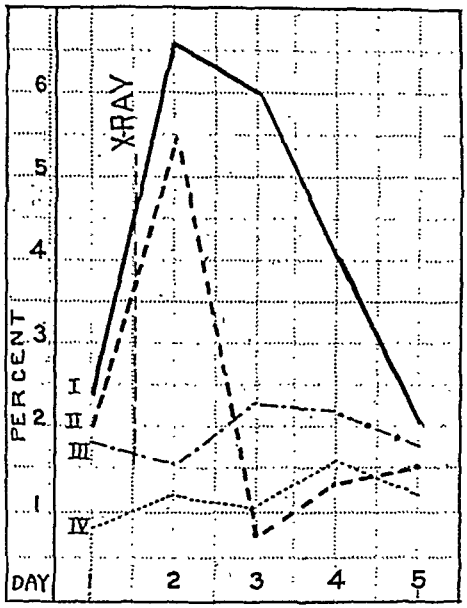


FIG. 2.—Diagram showing variation in percentage of granule red blood cells after Roentgen ray irradiation. I, II, and III are the three usual common types of change. IV, shows the variation in an untreated normal individual.

ated lesion. If the increase was temporary (twenty-four hours or less), and was followed soon by a decrease, the clinical results were those of too much irradiation, with a deleterious effect of varying duration on the patient's condition.

Source of Change in the Red Blood Corpuscles. The changes brought about in the red blood corpuscles appear to be the result of an effect on the cells and on the marrow rather than a change in the distribution of corpuscles in the circulating blood. Observations on Marathon runners[10] show that violent exercise with a consequent "stirring up" of the circulation did not appreciably change the percentage of young red cells, although the white cells

were definitely altered in number and kind. The changes in the blood cells following procedures calculated to "stir up" the circulation were studied by Drinker, Drinker, Kreutzmann[11] and by Schneider and Havens,[12] with the conclusion that changes in the volume or intensity of the circulation were not an adequate stimulus to dislodge immature blood corpuscles from non-hyperplastic bone marrow. However, differences in the percentage composition of the circulating leukocytes may be influenced by admitting into the circulation cells apparently dormant in the liver, spleen and other internal capillary areas. The percentage composition of the recognizable kinds of red cells does not appear to change proportionally. It seems, therefore, that the change in the number of young red corpuscles after irradiation is not one of redistribution of cells in different capillary areas.

The change after irradiation is very rapid, appearing in some cases after fifteen minutes of exposure. This takes place even without any significant change in the actual number of red blood corpuscles per cubic millimeter of the peripheral blood. At least any variation in the erythrocyte count is overshadowed by the normal percentage of error in counting red corpuscles. We have here an actual decrease or increase in the number of reticulocytes, with an increase or decrease in the number of granule red blood corpuscles. Some of the maturation changes may be brought about in the peripheral circulation and some in the bone marrow.

After the period of increased maturity of the red blood corpuscles a period of greater immaturity followed in some cases (Cases V, VII and X), with a rise in the number of reticulocytes. A similar change has been reported after intensive irradiation in the case of the white blood corpuscles[3] (Minot and Spurling,[8] p. 229). The change in the degree of maturity of the red cells and white cells corresponds to some extent to the reappearance of growth activity of irradiated cancer tissue, with the formation of multiple metastases, long after a radium or Roentgen ray treatment which has reduced the original focus to a quiescent state, the intermediate period varying with the type of tissue.

The increase in the number of reticulocytes which followed in some cases showed that the bone marrow must have been affected. The changes in the numbers and kinds of young red cells after irradiation with the short wave-length Roentgen ray indicates an apparent direct effect on the speed of the maturation processes. The first change after effective irradiation was an increase in percentage of the more mature red blood corpuscles, while the more immature decreased. This effect took place during irradiation, sometimes lasting for days, and at other times not much longer than the period of exposure.

The eventual increase in the number of red cells in many cases

of chronic myelogenous leukemia following irradiation treatment has been attributed to increased room in the bone marrow as the number of immature white cells decreased. The present observations, however, show that an additional factor is at work, as probably little change takes place in the number of white cells in the bone marrow during the first fifteen or thirty minutes of exposure of the body to irradiation. During this time the numbers of young red cells in the peripheral blood change markedly. The actual number of red cells per cubic millimeter may increase or decrease during the days immediately following irradiation. Within this period of time the change in number is seldom significant, rarely being more than 1,000,000 per cubic millimeter. Taking into account the fluid lost by the patient in vomiting and failure in some cases to replace it because of loss of appetite, and the inevitable loss of several pounds in weight during the period of treatment, the actual number of red cells per cubic millimeter of capillary blood gives little information as to the actual number of red corpuscles in the body.

Color Index. Although the total red cell count did not vary within significant limits immediately after irradiation, and frequently decreased temporarily during the week or two following, the color index rose in practically every case where the irradiation was effective, frequently increasing from less than 1 to 1 or more than 1. In 2 cases there was a fall in the color index immediately after the treatment. In both these cases a leukopenia developed in the following weeks (Case VII and one other of chronic myelogenous leukemia).

Relation to the Development of Leukopenia. Of those cases in which the data are complete, no leukopenia developed when the percentage of granule red blood corpuscles remained elevated for more than a day after irradiation. In Case VII the increase in number of granule red blood cells was definite after the first two exposures, but fell immediately after the third one. A leukopenia with 1400 white blood cells developed subsequently. If only one erythema dose had been given it is thought that sufficient irradiation would have been applied to produce the proper therapeutic result. Another case showed the wisdom of this procedure, so that when after one erythema dose the percentage of granule red cells began to decrease after having been elevated for less than two days after the second exposure, further treatment was suspended. Thus, while in some persons four exposures (two erythema doses, one anteriorly and one posteriorly) to the short wave-length Roentgen ray irradiation were necessary, in this second case the ideal results were produced by two.

Nature of the Irradiation Effect. The changes in the red cells from immature to mature suggest that a similar process may take place

in cancer tissue when it is irradiated. It seems more likely that the therapeutic irradiation effect is one of stimulation to go through the rest of the process of the life of the cell, reach maturity and die, rather than either of the alternate conceptions of a direct toxic or lethal action of the irradiation on the tissue.

The effect of the irradiation process is illustrated in Case XI, in which there was an increase in the number of granule red cells after irradiation during the period of regeneration after hemorrhage. From the point of view that this is an increase in the degree of maturation, the effect of Roentgen ray irradiation after hemorrhage is not detrimental. Watanabe and Harada,[13] considering only the reticulocytes and the nucleated red blood cells, naturally came to the opposite conclusion. They noticed the reduction in the number of reticulocytes and considered this as a depression of the bone marrow, following the usual interpretation, and advised against irradiation after hemorrhage.

Latent Period. Several phenomena after irradiation can be accounted for, if one takes the point of view that irradiation stimulates the cell to go through the rest of its life processes. Thus, there is always a "latent period" between the time of exposure and the time in which retrogressive effects are noted. It is the period in which the cell is becoming mature and reaches the height of its physiological development. When the cell becomes senile and approaches death the retrogressive effects are noted.

In the case of the red blood cells this period is extremely short. In the development of the white blood cells the process appears to be a little longer than in the red cells. With cancer tissue, as in carcinoma of the breast, no change may be noted in some cases for two weeks or longer. A histological study of irradiated cancer tissue shows that very little change takes place immediately. Double vital staining with neutral red and Janus green suggest that the cells go through a process very much like that of normal cells as they go through from youth to age. Thus Prigosen[14] has shown that the mitochondria decrease, while the neutral red-staining granules in the cancer cells increase in number during the periods succeeding irradiation, a process which can be interpreted from its analogy to the development of embryonic tissue as one of progress from youth to senility. The histology of therapeutic irradiation effects is not one of immediate necrosis. Nakahara[15] was able to find no microscopic evidence of direct injury of irradiation on tissues. This is also compatible with the observations described by Loeb[16] and others, of the comparatively greater resistance to irradiation of such mature tissues as adult muscles, ganglia and nerve fibers, over the more embryonic types. The resistance of birds' nucleated red blood corpuscles[17] is similar, as these cells are mature and are not analogous to the nucleated red

cells of man. Those cells which have already developed to maturity are more resistant, probably because the mechanism for development, division and differentiation can no longer be stimulated.

"Stimulating" and "Depressing" Doses. Small doses of Roentgen ray or radium irradiation are said to stimulate, and large doses depress. This has been described in connection with cancer tissues, plants and microörganisms. Bock[18] reported an increase in red blood cells after small doses, and decrease, with the appearance of immature forms in the circulation, after large doses. It is quite conceivable, however, that if a very slight stimulation were applied to growing cells, the cells would not necessarily be stimulated to complete their growth all the way to maturity, but would go on in their dividing process at a more rapid rate. The reproduction stage has usually been considered the critical one, although this is not necessarily true.[16] Alberti and Politzer,[19] on the basis of their experiments, conclude that, after irradiation, it is not the damage to the cells in the state of full mitosis which causes breaking down of the tissue, but it is the effect on the resting cells. The action, although not visible histologically at the time, is shown in a postponement of the cell division with more or less pathological mitosis which eventually leads to necrosis of the cells.

From the "increase maturation" point of view, all the effects of Roentgen ray irradiation are "stimulating." If irradiation is weak, the reproduction process continues but at a more rapid rate. If the stimulation is greater, the process of maturation goes on to completion, the rate and degree depending upon the strength of the stimulus. The cell passes the dividing stage, reaches maturity and dies. These effects of irradiation are what have usually been called the "stimulating" and "depressing" doses.

After the application of irradiation of certain intensities (greater than the stimulating dose but less than the depressing dose) to cancer tissue or to living organisms, no change may be apparent (Loeb,[16] p. 238). This seems to be true in those cases recorded here (Cases IV, V and IX) in which no effect was noted on the blood corpuscles or in the clinical condition of the lesion irradiated. The rate of stimulation under these circumstances apparently does not differ from the rate of stimulation affecting the body tissues at the time of the application of the irradiation. The young red blood corpuscles act similarly to the other tissues when the effective strength of the irradiation dose differs.

The Effect of Irradiation Not Specific. A study of the data brings out the fact that Roentgen ray irradiation does not cause any specific or peculiar change in the character or relative number of the red blood cells. All the variations are of a type that occur spontaneously in disease, with fever, with other types of therapy and with hemorrhage or transfusion. Sabin, Austrian, Cunningham

and Doan[20] noted that following transfusion there was first a slight increase in the degree of the maturity of young white cells in subacute myelocytic leukemia. Isaacs[21] had noted a similar change on the part of young red cells after blood transfusion, an effect very similar to that after irradiation therapy.

The increase in the degree of maturity of the red blood corpuscles in Case IX after some of the blood transfusions and after Roentgen ray irradiation during the same period, with the absence of effect of both agencies at other times, corresponds to the clinical reports of their effects on the red blood corpuscles of pernicious anemia patients. It is well known that a remission may be started sometimes after blood transfusion in pernicious anemia, but there are times when the course appears to be uninfluenced. Similar reports have been recorded after the use of Roentgen ray or radium irradiations over the spleen and long bones in this disease. Minot and Lee[22] noted beneficial results soon after Roentgen ray irradiation in 6 out of 10 patients. Bucky and Guggenheim[23] and Tomaner[24] had similar experiences, and other authors[25, 26, 27] report increases in the red blood cell count after irradiation of patients with secondary and aplastic anemia.

Irradiation stimulates in susceptible cases changes which are normal in the life of red cells, only the rate and time of initiation being changed. The same appears to be true of the effect of irradiation on leukocytes and on cancer cells. The maturation processes, once started, may continue long after the source of irradiation is removed, and death results from senility.

Summary and Conclusions. 1. Irradiation stimulates in susceptible cases changes which are normal in the life of a red blood corpuscle, the rate and time of initiation only being changed.

2. Effective short-wave Roentgen ray irradiation over any part of the body in man may be followed, in from one to twenty-four hours, by one of three responses of the young red blood cells. The granule red cells (corpuscles showing only a refractive granule) may show an appreciable and sustained increase in percentage, or the increase may be very transient or it may be negligible. Where there is an absolute or relative increase in the percentage of granule red cells there is frequently a decrease in the absolute and relative percentage of reticulocytes, unless the marrow is hyperplastic (hemorrhage).

3. Cases of cancer and leukemia, in which the increase in granule red corpuscles after irradiation is significant and sustained (two or more days), show a definite clinical improvement, and no leukopenia develops. In those cases in which there is no evident increase in the granule red corpuscles after irradiation, there is usually no clinical improvement in the irradiated lesion. If the increase is temporary (twenty-four hours or less), and is followed by an

abrupt decrease, the results are those of too much irradiation, a leukopenia develops, and the patient may become worse clinically.

4. In terms of degree of red cell maturity, clinically effective Roentgen ray irradiation causes an increase in the degree of maturity of the red corpuscles liberated into the peripheral circulation, starting during the period of exposure and lasting for from one to four days. This may be followed by an increase in some cases in the more immature red cells (reticulocytes).

5. The most frequent effect on the count per cubic millimeter of the red blood corpuscles in the peripheral circulation is a gradual temporary decrease, with an increase in the color index, which often becomes more than 1.

6. The change in the percentage of immature red corpuscles is one of orderly stimulation to reach maturity, through an effect on the cells themselves in the bone marrow and possibly in the blood stream. It takes place quickly, without an appreciable variation in the red blood cell count, and is different from the changes following redistribution of the cells in the peripheral vessels.

7. The percentage changes of the immature blood cells follow therapeutic irradiation over any region of the body, and appear to be a "systemic" effect of localized exposure.

8. The changes in the relative percentage of young red blood cells after therapeutic irradiation are similar to those taking place after blood transfusion.

9. The period between the application of the irradiation and the beginning of definite maturation changes in the red blood cells ("latest period") is probably a matter of minutes, as compared with hours or days for the leukocytes and weeks for carcinoma tissue.

10. Other points of similarity between the red blood cell changes after effective irradiation and those of cancer tissue are: (*a*) Development toward maturity and senility; (*b*) occasional period of immaturity subsequently; (*c*) so-called "stimulation" by weak doses and "depression" by large doses, with occasional absence of effect after irradiation of intermediate intensity.

11. From the evidence of the effect of irradiation on young red blood cells, all Roentgen ray irradiation may be considered as stimulative. Small doses may stimulate to division, large doses may stimulate to maturity and to death from senility, the rate for each tissue varying with its specific growth properties.

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ASSOCIATION OF DIABETES INSIPIDUS WITH OSTEITIS FIBROSA POLYCYSTICA.

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Neither diabetes insipidus nor generalized osteitis fibrosa polycystica is of frequent occurrence. In fact, the association of these diseases in a single patient has been observed so infrequently that the report of such a case appears to be justified.

Futcher[1] found 7 cases of diabetes insipidus recorded among the 403,535 admissions to Johns Hopkins Hospital from 1889 to 1904; among 370,000 admissions to the Mayo Clinic,[2] but 34 patients had diabetes insipidus. It was diagnosed as occurring in 17 of 35,492 patients treated in the medical clinic at Zürich[3] between the years 1867 and 1879. Gerhart[4] reported 55 cases recognized among 113,600 patients admitted to the Charité in Berlin during a period of twenty years. Thus, from a total of 900,000 hospital admissions, this disease was reported as occurring but 113 times. There is reason to believe that while diabetes insipidus is of rare occurrence in dispensary and private practice, it is, nevertheless, somewhat more common than is indicated by hospital statistics.

It is impossible to speak with accuracy as to the frequency of osteitis fibrosa polycystica. In 1910, Bloodgood[5] was able to collect from his own practice and from the literature but 12 cases of osteitis fibrosa, while Morton[6] writing in 1922, could tabulate but 63 cases of bone cysts of which 12 had been already included in Bloodgood's series. Of Morton's group, but 22 appear to have been cases of polycystic osteitis fibrosa. Schoen,[7] on the other hand, does not regard osteitis fibrosa as very rare.* This author has reported a case of degenerative bone disease associated with diabetes insipidus and corresponding more closely to the case which we are about to report than does any which we have found on record. Schoen[7] is of the opinion that osteitis fibrosa and Paget's disease cannot be differentiated one from the other. He bases this belief upon the following premises: (1) The pathological processes appear to be identical both in the gross and in histological structure; (2) clinical differentiation is, as a rule, impossible; (3) combination forms exist. Several hundred cases of Paget's disease have been described. Schoen[7] reports his case under the title of Osteitis Deformans (Paget) associated with Diabetes Insipidus and Nervous and Endocrine Disturbances. The existing confusion in nomenclature is thus made apparent.

* Two cases have been observed in the autopsy room of the Philadelphia General Hospital in the past five years.—Ed.

As to the excessive rarity of the association of diabetes insipidus with degenerative bone disease, there can be no doubt. A somewhat extensive search of the literature has enabled us to quote but 10 cases in addition to our own. These cases are as follows: (1) A group of 7 cases in each of which the syndrome of diabetes insipidus was associated with defects in membranous bones. Of these cases 3 were reported by Hand,[8] 2 by Schuller,[9] 1 by Christian,[10] and the last, in 1923, by Grosh and Stifel.[11] (2) Both polyuria and osteomalacia occurred during the course of pregnancy and form the subject of a case report by Gentili;[12] but both polyuria and osteomalacia in this patient disappeared after delivery. (3) Daser[13] reported a case of Paget's disease associated with daily urinary output varying from 1100 to 3500 cc. A diagnosis of associated diabetes insipidus cannot be based with certainty upon the data included in the author's report. (4) Schoen[7] reported in December, 1924, the case of Paget's disease associated with diabetes insipidus to which report reference has been already made.

Case Report. D. M., a white male was born September 9, 1921. His weight at birth was $8\frac{1}{4}$ pounds, and delivery was normal. He was first seen by one of us, (Gordon), October 16, 1924, at which time the child's chief complaint was excessive thirst and polyuria. At age of twenty-one months, an injury to the head occurred; at the area of impact there developed almost immediately a lump "about the size of a quarter dollar." This lump gradually increased in size until about four months after injury when child was operated upon by Dr. L. H. Landon, who made a diagnosis of hematoma with partial necrosis. Landon now believes that the tumor was a bone cyst. Two weeks subsequent to operation, the child developed difficulty in walking. He would scream with pain when he attempted to stand and soon gave up such attempts. He was referred to Dr. David Silver. A diagnosis was made of degeneration in first lumbar vertebra and in ilium. The outer table of ilium was found to be absorbed, there being present a small cavity about 2.5 cm. by 1.3 cm. The surrounding bone seemed hard. A small amount of broken down tissue and apparent granulation were removed by curettement after which a body cast was applied. The child remained in this cast for a period of six months, at the end of which the cast was removed and a body brace substituted. While the cast was worn, vomiting, which had been of occasional occurrence since the time of the head injury, became progressively more frequent. It appeared to be of propulsive type and soon occurred regularly during the night and during the course of the following morning. There was marked anorexia and the child rapidly lost weight. Vomiting stopped after removal of the cast.

Excessive thirst and polyuria were first noted in March, 1924, or nine months after the head injury. In the beginning of this phase of his disease, the boy would drink about 1 liter of water

during the night. Water intake gradually increased until he was drinking 8 to 12 liters of water during the twenty-four hours. Urine output paralleled the water intake, as much as 4 liters being excreted during the course of a night.

Physical Examination. October 16, 1924. A child of marasmic appearance, aged thirty-seven months, whose mother desires that he be treated for excessive thirst. The child is wearing a body brace, is underweight, his skin is dry and wrinkled, the musculature is flabby and poorly developed. There is present a dry seborrhea of scalp; and a scar over left eye with ptosis of upper lid. The pupils are round and equal and react to light and accommodation; there are no extraocular palsies, the ptosis having obviously resulted from operation. The tonsils and cervical lymphatic glands are enlarged; there are no demonstrable abnormalities respiratory or cardiovascular systems. The abdomen bulges with protruding umbilicus, but is otherwise negative.

Bones and Joints. The surface of the skull is markedly uneven because of numerous elevations from split pea to quarter dollar in size. Supraorbital prominences are markedly overdeveloped, the right larger than the left. The fontanelles are closed. There are no demonstrable deformities of ribs, vertebrae, pelvis or bones of extremities; no massiveness of the inferior maxilla; the hands and feet are of ordinary size for this age.

Laboratory Findings. Urine examination: October 16, 1924, total quantity in twenty-four hours averages 8 to 12 liters. A mixed specimen shows: Specific gravity 1002; no albumin, sugar, Bence-Jones protein, or acetone. The blood picture is normal with hemoglobin of 90 per cent; the Wassermann blood test is negative and a like reaction was subsequently obtained on the blood of each of the child's parents.

Dr. David Silver kindly furnished us with the following note as to the clinical diagnosis of the bone disease, together with a laboratory report on the nature of the material removed by curettement. "The disease process present in ilium is apparently an osteitis fibrocystica. Tissue removed from ilium looks like an old pyogenic osteitis of outer table." The report on the specimen referred to the Singer Laborabory is as follows: "A tiny fragment of soft tissue, which was fixed in Zenker's fluid. On microscopic examination this was found to be very cellular. A small piece of compact bone is attached to one side. The cellular portion appears to occupy the medullary part of the bone. Two types of predominating cells are present. Of these, the more numerous are cells about the size of a large lymphocyte or lymphoblast, having a pale oval nucleus and rather abundant pale cystoplasm, sometimes clear or vacuolated. These cells are closely packed with little or no stroma; yet there is no definite architectural arrangement. Several mitotic figures are found in the cells of this type. Situated generally toward the periphery of the

groups of cells above described, are found groups of small lymphocytes, and, scattered irregularly throughout, are numerous eosinophilic leukocytes with an occasional small focus of neutrophilic polymorphonuclear cells. The general make up of the tissue, as to predominance of one type of cell with mitotic figures, is consistent with a diagnosis either of tumor or of an infectious process; but we do not feel that we can make a positive diagnosis from this specimen. The type of cell is consistent with lymphoblastoma or nongranular myeloma. No normal myeloid tissue is seen; no evidence of cyst."

Subsequent Case Record. On October 16, 1924, the patient was given a hypodermic injection of 0.5 cc. of commercial pituitrin, the water intake during the subsequent twenty-two hours being reduced to $3\frac{1}{2}$ liters. On the following day the child received 0.5 cc. of pituitrin, the water intake being 2 liters for the succeeding twenty-two hours. Medication was withheld during the following two days during which time the water intake rose to 7 liters in twenty-four hours, and vomiting, which had stopped following the first injection, recurred and was severe. On October 20, 0.5 cc. of pituitrin was injected and the water intake for the subsequent fifteen hours was one liter. Subsequent to this observation 1 cc. of pituitrin has been administered on alternate days. This dosage has been found to control the polyuria for a period of thirty to thirty-six hours. While under the influence of pituitrin child showed marked subjective and objective improvement: his appetite improved and restlessness and vomiting disappeared. In a few instances pituitrin was withheld longer than forty-eight hours, always with the return of polydypsia and polyuria, loss of appetite and increase of irritability.

Radiographic Report. The material studied comprises radiograms of practically the entire body. These were made in July, 1924 November, 1924, and again in March, 1925.

In the right lateral view of the skull are four areas of bone absorption clustered in the fronto-parietal region. They are approximately 1.5 cm. by 1 cm. Five similar areas are found in the left lateral view. The largest of these, 5 cm. by 4.5 cm., is located in the lower frontal region. Two smaller ones are nearer the midline anterior to the fronto-parietal suture, and two 1 cm. by 1 cm. are in the upper occipital region. There is no evidence of abnormality in the region of the sella turcica in any of the films of the three series.

The glenoid processes of both scapulae show from three to five areas of rarefaction which are approximately 0.5 cm. in diameter. There are no abnormalities present in the ribs. The epiphysis of the greater tuberosity of the left humerus contains five small areas not more than 0.2 cm. in diameter.

The body of the first lumbar vertebra is greatly reduced in size; there is no rarefied area surrounded by normal bone. The appear-

ance would lead one to suspect that an earlier cyst had been replaced with fibrous tissue, and with subsequent decrease in the size of the vertebra.

From five to seven areas of bone absorption are found in each ilium, and in both sides of the sacrum; the left ischium shows many small areas of bone absorption: the right ischium but one.

The epiphysis for the head of the right femur reveals a circular area of lessened density about 1.3 cm. in diameter. The necks of both femora show larger areas. In the upper third of the shaft of the right femur, a central lesion, 1.2 cm. by 2 cm. that has produced expansion of the cortical bone, is present.

The general appearance of these lesions is that of a rarefied area surrounded by normal bone. They are essentially regions of bone absorption or of bone destruction without evidence of repair. The periosteum is not involved. The absorbed areas appear as cyst-like formations within the medullary cavity.

Comparing the three sets of films, we note a progressive improvement in the bone disease. The progress between November, 1924, and April, 1925, has been greater than that between July and November, 1924.

The age of the patient, the multiplicity of the lesions, the peculiar distribution and the mottled appearance of the bones would suggest a diagnosis of a polycystic osteitis.

The absence of new bone formation eliminates osteomyelitis.

The uninvolved bone shows no marked osteoporosis. Osteoporosis is usually present in osteomalacia. Osteitis deformans occurs at later age periods. The characteristic thickening of the subcortical bone in Paget's disease is absent here. Multiple giant-celled tumors do not occur in the first age period, nor do they produce so many lesions.

The multiplicity of lesions is evidence against central sarcoma. No mention is made in the literature of cysts in multiple myeloma. True enchondromata are extremely rare in the long bones.

The multiplicity of the lesions also rules out the acute infections, tuberculosis and syphilis.

Recapitulation of Roentgen-ray Report. A study has been made in a three-year old male of bone tumors or bone cysts with involvement of the cranium, the shoulder girdle, the long bones of the arms and legs as well as the flat bones of the pelvis. The tumors or cysts appear as areas of bone absorption surrounded by normal bone. The periosteum is not affected. The epiphysis as well as the diaphysis is the seat of disease. The distribution, multiplicity and mottled character of the lesions is favorable to a diagnosis of osteitis fibrosa polycystica.

Summary of Case Report. A child previously normal, at the age of twenty-one months received a head injury. At the area of contact a swelling developed which was probably at the outset a

hematoma, but which when operated upon four months later, was found to contain tissue which was apparently necrotic. The operating surgeon believes that at this time the tumor was a bone cyst. Two weeks subsequent to operation there was obtained evidence of involvement of first lumbar vertebra and ilium, involvement of other bones being noted from time to time. Examination of a fragment of tissue curetted from the diseased area in the ilium failed to lead to histological diagnosis, but Dr. David Silver believed that clinical evidence supported a diagnosis of osteitis fibrocystica. Radiographic examination of individual bones, or of the entire skeleton, was made at intervals and the radiographer believes that upon the results of these Roentgen ray findings alone a diagnosis of osteitis fibrosa polycystica can be made. Comparison of earlier with later radiograms shows that the bone disease has lessened in severity during the period of observation.

Diabetes insipidus developed nine months after the head injury and at a time when the generalized disease of bone was well advanced. It was found that the polydypsia could be controlled by hypodermic injections of pituitrin. One cc. has been injected on alternate days throughout a period of eight months during which time the child has shown marked subjective and objective improvement.

Discussion. The occurrence of diabetes insipidus during the course of a disease associated with multiple bone lesions naturally leads to inquiry as to whether the association is accidental or whether the diabetes insipidus arose as a result of the bone disease or whether the occurrence of both affections was merely due to the presence of a common cause.

Such inquiry must naturally take into consideration the etiology of osteitis fibrosa polycystica and of diabetes insipidus. Unfortunately, the cause of neither of these affections is fully known. The existence of osteitis fibrosa polycystica as an entity apart from osteitis deformans has been questioned. Diabetes insipidus is a clinical syndrome only.

Many theories have been advanced as to the causation of osteitis fibrosa polycystica. Virchow[14] believed it due to cystic degeneration and absorption in enchondromata. Boit[15] stated that most cases of osteitis fibrosa are of inflammatory origin, the others being caused by toxic agents resulting in disturbance of metabolism which in turn brought on the bone changes through the action of abnormal secretions. Rehn[16] likened the disease to hog snuffles, a phase of dystrophy in rapidly growing bones. Silver[17] and Landon[18] conclude that the cyst formation arises as the result of one of three processes—infectious, neoplastic or metabolic. McCrudden[19] writes that formation of bone cysts may be due merely to nutritive unbalance which results in calcium withdrawal, the increased catabolism of bone possibly originating through a need for calcium in other body structures. He finds that foods

low in calcium do not decrease calcium output, the resulting calcium unbalance eventually resulting in softening of the bones. Barrie[20] believes that the cystic areas are caused by a contraction of granulation tissue. He regards bone cysts, osteitis fibrosa and giant-cell sarcoma as but different phases of the same process: an attempted repair following bone destruction, the latter being probably induced by infection, trauma, malnutrition or metabolic changes due to endocrine disturbances. Von Recklinghausen[21] in his original communication states that in his belief the peculiar bone changes are a result of traumatic or mechanical factors: fibrous tissue, cyst formation and giant cell sarcoma representing different phases of the same process, namely, an attempt at repair. Lotsch[22] concludes that the underlying basis for osteitis fibrosa is a disturbance in the correlation between the glands of internal secretion. He demonstrates by animal experiments that in his series a hematoma did not lead to cyst formation. Therefore, he rejects the theory of traumatic origin of bone cysts.

That a complex association of diffuse bone disease may occur with diseases ordinarily attributed to metabolic disturbances or with diseases of ductless glands is exemplified by a case reported by Young and Cooperman[23] in which osteitis fibrosa polycystica was associated with giant cell sarcoma. In this patient a diagnosis was also made of rickets and of tumor of the hypophysis. Schoen[7] states that osteitis deformans, under which term he includes osteitis fibrosa, is often associated with dysfunction of the ductless glands. Of 11 cases of chronic bone disease associated with clinical evidence of endocrine disturbance, he finds that premature appearance of menopause occurred in 7, giantism appeared in 2, and enlargement of thyroid in 3. In 1 member of the latter group hypothyroidism was present. He believes that these combinations of disturbances of internal secretions with Paget's disease are not accidental. The special relationship of hypophysis with ovaries and bony growth is recognized. The relationship of another generalized bone disease, osteomalacia, with pregnancy and the fact that oöphorectomy or Roentgen ray treatment of the ovaries can exert a favorable influence on osteomalacia are cited as observations which support the general contention. O'Meyer and Schmorl are quoted as having described tumors of hypophysis as occurring in cases of Paget's disease reported by them. "It can only be stated that there exists a connection between changes in the glands of internal secretion and the bone disease: the problem as to the etiology of osteitis deformans is not solved thereby."

Theories as to the causation of diabetes insipidus abound. The syndrome has been noted in association with systemic bacterial infections, with encephalitis lethargica, head injury, tumor of brain or hypophysis, intoxication as occurring in pregnancy or hyperthyroidism, syphilis and tuberculosis. Heredity has been thought



FIG. 1

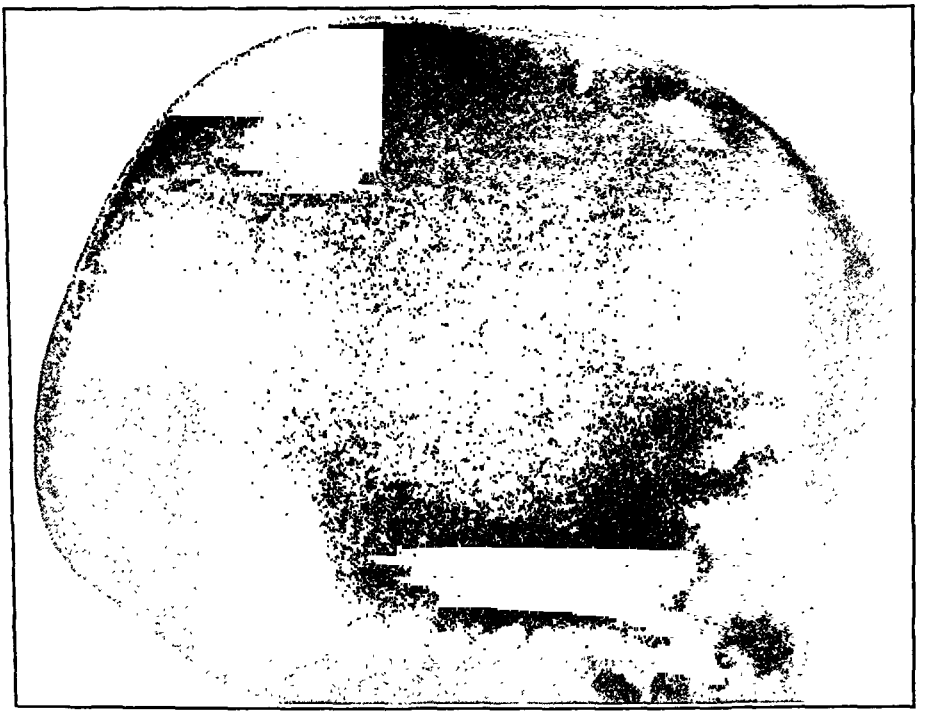


FIG. 2

FIGS. 1 and 2.—Multiple areas of bone absorption (Polycystic osteitis) in the frontal, fronto-parietal and occipital regions of the skull. Sella turcica normal.



FIG. 3.—Similar areas involving both scapulæ.



FIG. 4.—Involvement of the sacrum, ilia, ischia, and heads of both femora.



FIG. 5.—Note the lesion in the epiphysis for the head of the right femur. In the upper third of the shaft of the right femur there is a central lesion showing expansion of the cortical bone.

orthopedist, whose attention is especially directed toward disease of bone, may fail to notice or record polydypsia and polyuria. In other words, an association of these disorders may be more common than is indicated by case reports.

It is our belief that in our patient, as in Schoen's,[7] the association was not accidental. Whether the initial head injury were responsible for the generalized osteitis fibrosa or for the diabetes insipidus or for both, must remain an open question. Authors have been quoted who believe that each of these conditions can be produced by cerebral trauma. Lotsch's animal experiments merely prove that bone cyst did not follow hematoma under experimental conditions in the animals studied by him. His conclusions must be accepted with reservation as applied to man.

Dysfunction of the ductless glands has been evoked as one of the etiological factors in producing generalized bone disease, and it is also given a prominent place among the etiological factors of persistent polyuria. There is some clinical and experimental evidence to support this view. This evidence is stronger in the case of diabetes insipidus than in that of generalized degenerative disease of bone, but even in the former instance the supposition as to the etiological influence of disturbances of internal secretion is perhaps as acceptable as any. The prompt control of our patient's polyuria by hypodermic injections of pituitrin, together with the roentgenological evidence as to the improvement of the osteitis fibrosa during the period of pituitrin administration may be mentioned as clinical observations which offer some support to the supposition that deficiency of the pituitary hormone may have played a part in bringing about both of the conditions named.

Is roentgenological evidence that a sella turcica may cast a normal shadow proof that no disturbance of pituitary hormone exists? To this question one may unhesitatingly answer in the negative. It is probable that not only the hypophysis but also the pars tuberalis and a portion of the hypothalamus immediately contiguous with the upper part of the hypophyseal stalk possess like functions to those of the posterior lobe and pars intermedia of hypophysis. It is possible that they possess like functions to those of the anterior lobe as well. In other words, these structures exercise some control over urinary excretion; they may also regulate to some extent the function of bony growth. If this be true, then modification of hypophyseal function may occur in the presence of a structurally normal hypophysis.

Clinicians have frequently observed that diabetes insipidus first appeared after head trauma. We have in our case a history of trauma; but the late appearance of diabetes insipidus would indicate that the latter was not directly due to the initial skull injury. In the patient described by Schoen[7] it was noticed that the base of the skull was extremely massive and compact. Sinuses were not defi-

nitely recognizable and the roof of the skull was strikingly thickened. The sella turcica showed no decrease in size, but the occurrence of polyuria is attributed to abnormal bony growth in the region of the hypophysis, thickening of the skull occurring at the expense of the size of the cavity. Such thickening of bone was not shown in our case, but the possibility of its existence cannot be denied. Therefore, may it not be accepted as a reasonably satisfactory hypothesis, as perhaps a guess not susceptible to proof, that in our patient hematoma following injury to the skull was succeeded by local bone cyst, that there followed, because of influences not at present understood, a generalized osteitis fibrosa, and that as a result of this bone disease, there resulted alteration in hormones supplied by the hypophysis and other structures with which it is physiologically allied? If this hypothesis be correct, then the occurrence of the diabetes insipidus is explained.

Summary. A case is reported in which occurred the exceedingly rare association of osteitis fibrosa polycystica with diabetes insipidus. The generalized bone disease followed local trauma to skull. The polydypsia and polyuria did not appear until the osteitis fibrosa was well advanced. We have speculated as to whether the association was accidental, whether bone disease and diabetes insipidus were due to the presence of a common cause, or whether the bone disease was indirectly responsible for the persistent polyuria. This report is made in the hope that it may eventually throw some light upon the obscure etiology of both osteitis fibrosa and of diabetes insipidus.

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THE HUMAN CEREBROSPINAL FLUID IN SYSTEM AND DIFFUSE DEGENERATIVE DISEASE INVOLVING THE NERVOUS SYSTEM.*

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There are very few of the degenerative, infectious or system diseases in which careful and consistent studies of the spinal fluid have been undertaken. For the most part, reports in the literature cover isolated cases and one always questions their reliability, since other physical factors may not have been considered. The only evidence admissible upon which conclusions may be based comes from those who have made a group study of some special condition and reported all the findings from both clinical and laboratory standpoints. From such materials, one is reasonably safe in tabulating statistics.

Multiple Sclerosis. Few other conditions conscientiously investigated thus far have revealed the marked cerebrospinal fluid findings that are reported in multiple sclerosis. Ayer and Foster[1] reported the findings in 38 verified cases in 1921. They found no pressure alterations beyond the normal. The cell counts in 48 specimens of fluid showed 0 to 5 cells in 61.2 per cent, 6 to 10 cells in 16 per cent 11 to 20 cells in 4.2 per cent and 42 cells in 2 per cent.

The total protein showed an increase in 50 per cent of cases; the globulin reaction was negative in 22 cases and positive in 9. The Wassermann reaction was negative throughout. The gold-chlorid test gave more definite findings than any other estimation. Forty-two readings were made, showing a "paretic" type of curve in 21 fluids (16 patients), a "luetic" type in 7 fluids (7 patients), positive reactions in 3 fluids (3 patients) and negative reactions in 11 fluids (10 patients). This shows that the "paretic" curve

[1] * Read before the Association for Research in Nervous and Mental Diseases, December, 1924.

was obtained in one-half the number of fluids examined and nearly one-half the number of cases.

Sugar averaged 0.048 per cent in 14 fluids. Nonprotein nitrogen averaged 21.5 mg. in 11 determinations. The average in 11 determinations of chlorid content was 688 mg. per 100 cc. No acetone bodies were found. Creatinin averaged 1.78 per 100 cc, and urea 15.5 mg. per 100 cc.

Eskuchen[2] found 3 out of 4 cases to have entirely negative fluids; the fourth case showed a pleocytosis, increase of globulin and a paretic gold curve. Jaeger and Goldstein[3] reported, in a few cases, a "slight colloidal-gold reaction, there being a faint color change in the first 4 to 5 tubes." Flesch[4] reports 8 cases, showing a completely negative fluid in 1 case, a slightly positive colloidal-gold curve with other tests negative in 1 case, and a paretic-gold curve in the remaining 6 cases. Kaplan[5] reported 2 cases in which one had a negative and the other a paretic-gold curve. Later, he reported 18 cases[6] in which but 1 had the paretic type of curve. Oetiner[7] found the globulin increased in 1 case with other findings negative, and 1 case with no pleocytosis or globulin but with a partial reduction in the colloidal-gold reaction.

Rolstadt[8] stated that in 75 per cent of cases there is no cellular increase in multiple sclerosis. Moore[9] states: "Together with the clinical evidence, it is believed that the spinal fluid picture is fairly constant and that, other things being equal, such a picture is a strong argument in favor of a diagnosis of multiple sclerosis. In its absence, the diagnosis becomes at least doubtful." Eskuchen[10] at a later date (1919) reported that multiple sclerosis in a large percentage of cases showed typical tabetic or paretic curves. Sicard[11] found 2 cases with a pleocytosis and 5 cases without it. Eskuchen[12] again states that the spinal fluid findings vary, 50 per cent showing a normal fluid. In 30 per cent of cases, the pressure was slightly increased, the globulin weakly positive, the cell count 20 to 30 and the gold reaction of the "luetic" type The fluid Wassermann reaction was negative. In about 20 per cent of cases the pressure was definitely increased, the globulin moderately positive, the cell count 30 to 50, the fluid Wassermann negative and the gold curve of the "paretic" type. Boyd[13] examined the fluids in 18 cases, finding the fluids clear, pressure normal, the cells varying from a slight to a moderate lymphocytosis, but never exceeding 30, and the globulin slightly increased. On the other hand, Mestrezat[14] found 3 fluids negative in every respect. Tucker[15] in 4 cases of multiple sclerosis, noted that the pressure varied in each case, that cells numbered not more than 5 and the gold curve was of the paretic type in only 1 case.

A review of selected hospital case records with serological studies and typical clinical syndromes, shows that the current literature is in agreement for the most part. Time did not permit the exhaustive

survey that the subject demands, and it is regrettable that necropsy confirmation is not obtainable in the majority of instances. However, basing conclusions on the material at hand, there were found: normal appearance and pressures of fluids, not infrequent cellular increases, occasional increases in globulin content, and gold-sol curves ranging from negative, atypical and luetic to paretic types. The paretic types occurred in less than one-third of all cases. Ayer and Foster[1] mention the variation in types of curves in the stationary and progressive cases, finding the paretic type most commonly in the latter. To this observation, there might be added the age factor, for in 6 cases personally observed where definite clinical symptoms were present, the indefinite or negative curves were found in patients between fifteen and thirty years of age, while the paretic curves were the rule in the thirty to forty-five age periods. This naturally raises the question of the time of onset of the disease and whether it might not originate at a much younger age period than we are led to believe by the usual histories.

The figures for sugar content have varied remarkably and show no uniformity. The same is true of the protein constituents of the fluid. These two substances have no apparent relationship to the colloidal-gold reaction. In a few cases in which the chlorids were estimated, they were found high, usually over 600 mg. per 100 cc.

The Encephalitides. Few studies are reported in spinal fluids of cases of encephalitis. Frequently the type of encephalitis is not known, the term used being merely "acute encephalitis." This does not lend itself to conclusive survey reports. However, in those cases reported, some findings are worthy of mention. Sicard[11] reported no other findings than a marked polynucleosis. Eskuchen[12] stated that in pure encephalitis, no changes in the fluid could be found, except where meningitis coëxisted and then the typical findings of meningitis were present. Polioencephalitis had no effect upon the fluid findings.

In epidemic encephalitis many reports have been made, in fact the figures from some thousands of cases are available. The findings may be said to be consistent only in their inconsistency.

Bassoe[16] reported clear fluids under increased pressure, globulin slightly increased, but the colloidal-gold reduction in the luetic zones in practically all cases.[18] The cell count varied, being less than 10 in 6 cases, 10 in 1 case, 25 in 1 case and 26 in 1 case. Neal[17] studied 40 cases. She found the cells to be slightly or moderately increased, occasionally reaching 150 to 200; lymphocytes predominated. It was further noted that the cell counts fell off very quickly. Globulin was greatly increased. The gold curve was of the luetic type in some cases, but was not common. Sugar was increased in amount.

Brill and Benson[18] in a study of 13 cases with special reference to the Lange reaction found a reduction in the luetic zone in all

cases. Flexner[19] in a general investigation of this disease, noted an increased pressure of the fluid, which was clear. The number of cells were slightly increased—rarely reaching 100 to the c.mm., but usually around 10 to 20, and mostly of the lymphocytic variety. He found also that globulin was slightly increased.

Davis and Kraus[20] reported the findings in 34 cases. Here 42 per cent showed changes in the gold curve, usually in the luetic or meningitic zone. There was no relationship between the stage of the disease and the gold solution readings. Two cases showed a paretic type of curve. They finally concluded that "abnormal colloidal-gold reactions are evidence of pathological changes and not of specific etiology." Later, Kraus and Pardee[21] summed up the reports to that time, for presentation before the Association for Research in Nervous and Mental Diseases. In their review of the literature, Von Economo and Neal are quoted. The former found an excess of globulin, the cells ranging from normal to 43, the pressure increased in some cases and the colloidal gold negative. The latter pointed out abnormal changes in the gold curve and mentioned the similarity of the curve to poliomyelitis. Following this, observations on the occurrence of syphilitic and paretic types of curves were made by Bassoe, Brill and Benson, Davis and Kraus, and Archambault.

The fluids were reported as clear and colorless in the majority of cases but "bloody fluids have occasionally been found, in fact more commonly than could be accounted for by the puncture of a vein." The pressure varied from normal readings to a considerable increase. The cell counts found by the French differed from those of Von Economo. The French stated that a normal cell count was a rule and was of diagnostic significance. The English and American observers, however, have found a pleocytosis. The cells are predominantly of the mononuclear type. "The impression gathered from the literature is that the number of cells may vary from normal to an increase of several hundred."

The globulin was increased in a majority of cases. Sugar, whenever reported, has exceeded the normal limit, figures varying from 0.067 to 0.106 per cent. The Wassermann reactions have been uniformly negative. The gold curve in Von Economo's report showed "no typical elevations."

The contribution of Kraus and Pardee then summarizes 245 cases. The fluid findings were as follows: (1) Clear, colorless fluids; (2) increase in spinal fluid pressure; (3) increase in number of mononuclear cells; (4) increase in amount of globulin; (5) increase in amount of spinal fluid sugar; (6) a negative Wassermann reaction; (7) the presence of bodies producing a change of a solution of colloidal gold (Lange).

The number of cells is greatest in the first three weeks of the disease. Fluctuation in the number of cells occurs during the

disease, an increase occurring in remission. The globulin was increased to a moderate degree in 72 per cent of cases. The sugar in 12 cases varied from 0.062 to 0.095 per cent. The Wassermann reaction was negative. The colloidal-gold curve was changed in 83 per cent of cases (100 out of 120 cases). The type of curve varies considerably, there being a tendency to elevation of the left hand part of the curve in later stages, but this was not constant. Changes did, however, occur in the middle zones.

TABLE I.—SPINAL FLUID FINDINGS IN ENCEPHALITIS.

Case No.	Pressure.	Cells	Globulin.	Wassermann reaction.	Colloidal gold.	Sugar, per cent.
1	Normal	2	+	Neg.	Neg.	
2	4 mm.	1	+	"	"	
3	8 mm.	7	+	"	"	
4	+	10	+	"	"	
5	Normal	5	+	"	"	
6	Normal	3	+	"	"	
7	+	1	+	"	"	
8	Subnormal	15	++	"	"	
9	Slow increase	3	+	"	"	
10	Slow increase	2	+	"	"	
11	Slow increase	12	+	"	"	
12	Normal	0	+++	"	2211100000	
13	++++	22	++++	"	Neg.	
14	+	0	++	"	"	
15	16 mm.	2	+	"	"	
16	+++	1	++	"	2110000000	0.07
17	12 mm.	11	+	"	Neg.	
18	Normal	10	+	"	"	
19	Normal	2	+	"	"	
20	+++	1	++++	"	"	
21	Slow increase	10	+	"	"	
22	+	20	+	"	"	
23	Normal	3	+++	"	"	
24	Normal	2	+	"	"	
25	Slow increase	12	++	"	"	
26	Normal	2	+	"	"	
27	Normal	2	Normal	"	"	
28	Normal	6	+	"	"	
29	Slow increase	7	+	"	"	
30	Increase	18	Normal	"	"	
31	++++	5	++	"	"	
32	Normal	3	++	"	"	
33	Slow increase	9	++	"	"	
34	22 mm.	0	Normal	"	"	
35	Normal	4	+	"	"	
36	4 mm.	5	+	"	"	
37	Normal	4	+	"	"	
38	40 mm.	50	++	"	"	
39	+	0	++	"	2221100000	
40	Normal	4	+	"	"	
41	+	5	+++	"	"	0.075
42	++	0	++	"	"	0.068
43	+++	0	++++	"	"	0.06
44	+	8	+++	"	"	
45	12 mm.	15	+	"	"	

Levinson[22] reported the fluids in encephalitis epidemica as colorless, with increased globulin, and cells usually increased to from 10 to 50. An increase in globulin without a corresponding pleocytosis was a not inconstant finding. Tucker[15] in a contribution to this compilation, reported on 45 fluids (see Table I). He found the pressure variable, being subnormal in 2 cases while it reached 50 mm. in 1 case. The cell counts ranged from 0 to 50; from 0 to 10 in 33 fluids; from 10 to 20 in 9 fluids; 20, 22, and 50 in 3 respective fluids. The globulin was normal in but 3 fluids; slightly to moderately increased in 35 fluids, and definitely increased in 7 fluids. The Wassermann was consistently negative. The gold curve was negative in all but 3 fluids, each of these showing a reduction in the left-hand tubes. Sugar is reported as negative in all but 4 cases, and here it ranged from 0.06 to 0.075 per cent.

Extracts from hospital records from various sources bear out the foregoing, and in particular the inconsistency of spinal fluid findings. In all cases the fluids were clear. The pressure, when recorded, was normal or moderately increased, the globulin either negative or + 1, occasionally + 2 and rarely + 3. The Wassermann reaction was consistently negative. The sugar content was not estimated in the majority of cases, but the few observations made showed a range from 0 to 0.110 per cent as the two extremes, while the most of them fell between 0.040 and 0.075 per cent, the average being 0.062 per cent.

In this connection the research of Alpers, Campbell and Prentiss[23] is of distinct significance. They found a great variation of spinal fluid sugar in a small series of normal cases and conclude that the normal content is as yet not correctly estimated. In epidemic encephalitis, they concluded from reports in the literature that there was considerable doubt as to the significance of increased sugar percentage. They studied the fluids from 35 patients with encephalitis and found an average of 82.1 mg. per 100 cc. This contrasted with an average of 45.3 mg., in untreated paresis; 55.4 mg. in treated paresis; 80.1 mg. in dementia precox; 66.9 mg. in manic depression psychoses, and 123 and 189 mg. in 2 cases respectively of diabetes. By considering the normal fluid to contain from 50 to 65 mg. of sugar per 100 cc, it is evident that their cases of epidemic encephalitis showed a distinct increase. The hospital records mentioned above would then indicate a normal sugar content.

The gold solution curves could in no sense be considered typical, except that in the majority of cases they were negative. Unfortunately, however, the stage of the disease is not mentioned in some instances, which precludes reliable conclusions.

Poliomyelitis. The first note appearing in the literature of spinal fluid findings in poliomyelitis is found in 1902 in an article written by Sicard.[11] In it he states that the cells are greatly increased in the acute stages and are mainly lymphocytes.

Gay and Lucas[24] in 1910 published the results of an experimental study of poliomyelitis in monkeys. They found in 6 cases of monkey poliomyelitis, that the cytology of the incubation period showed 100 to 300 cells. In the prodromal period, the cells rose to 100, and 60 per cent of them were polymorphonuclears. In the early acute stage cells were definitely increased but had a predominant lymphocyte percentage. At the end of a week or ten days, there were few cells left.

Abrahamson[25] reviewed the literature in 1912 and reported as follows: Forbes[26] studied 33 fluids of which 6 were bloody. Twenty-four had albumen in varying amounts, 6 a heavy precipitate. Twenty-one fluids had an increase in cells, the cellular elements being in direct proportion to the albumen content. Morse[27] examined 13 fluids, finding them all clear and cells increased in all of them. Abrahamson studied 43 fluids. Fifteen fluids showed a great increase of cells, 24 a moderate increase and 4 no increase. Small mononuclear leukocytes predominated in 88 per cent of cases. The albumen content was increased in 52 per cent of cases. He found no relation between the albumen-globulin ratio and the stage of the disease. The sugar was tested in 15 fluids, 12 giving a good reduction and 3 a weak reduction. Curiously enough, the fluids having a weak reduction were the most severe cases clinically.

The best article published on the subject was by Peabody, Draper and Dochez in 1912,[28] a monograph from the Rockefeller Institute. Sixty-nine patients formed the material for the study made and from these cases 233 fluids were obtained and examined. Their conclusions may be summarized as follows: 1. The fluids from the early cases of the disease and especially before onset of paralysis tend to show an increased cell count with a low or normal globulin content. At this stage, the polymorphonuclear cells may be 90 per cent of the total. Most fluids, however, show almost exclusively lymphocytes and large mononuclears. 2. After the first two weeks, the cell count usually drops to normal or nearly normal, and there is frequently an increase in globulin content. A slight increase in globulin may persist for seven weeks or even longer. 3. The fluids in abortive cases are analogous. 4. The examination of the cerebrospinal fluid in acute poliomyelitis, while giving as far as is yet known, no specific diagnostic criteria, is of the utmost value as an aid to diagnosis, both in the preparalytic and abortive cases.

Batten[29] agreed that results in fluid examinations in poliomyelitis were variable, but that some cases showed an excess of albumin, with a moderate increase of lymphocytes. In some cases a very large increase of cells was found. For the most part, the stage of the disease and its location influenced the findings, those cases with the most marked meningeal involvement giving most findings in the spinal fluid.

Hayne and Cepelka[30] studied 30 cases of poliomyelitis clinically,

including the examination of the cerebrospinal fluid. They found: (1) The pressure normal in 25 cases and slightly increased in 5 cases. (2) The cells varied from 8 to 98 averaging 30 to 50.3. The globulin was increased in 16 cases.

Kolmer, Freese, Matsunami and Meine[31] reported a study of 868 fluid specimens from poliomyelitis in the Philadelphia epidemic of 1916. The conclusions were: (1) The majority of fluids were of a watery color, 1 to 2 per cent only showing a faint turbidity. (2) Seventy-two per cent of fluids from all stages showed an increase of total cells; in 80 per cent of these cases the counts were not above 100 cells per c.mm. An increase in the total cells was found in the preparalytic stage and this increase was present in 95 per cent of cases for at least three weeks after the onset of the paralysis, after which the number of cells gradually decreased. (3) In over 96 per cent of the fluids from the onset of paralysis, small lymphocytes predominated. (4) An increase in protein was found in 32 to 42 per cent of fluids. (5) During the acute stages the fluids of 40 to 50 per cent of cases yielded a colloidal-gold reaction of luetic and meningitic zones types. (6) All fluids gave a negative Wassermann reaction.

Jeans and Johnson[32] found in 100 spinal fluids examined that the colloidal gold showed a definite reduction in the luetic zone in every case, regardless of the stage of the disease. No mention is made of the cellular contents of these fluids.

Felton and Maxey[33] examined 57 fluids. They reported: (1) In the acute stages of poliomyelitis, the spinal fluid reacts with colloidal gold in zone 2 of the curve (dilutions 1 to 40 to 1 to 160), that is, in the luetic zone. (2) In the second and third weeks, the reaction is practically the same as in the acute stage with a tendency to clear up in some cases and a precipitation in the higher dilutions in others. There is no constant rule. (3) In the fourth to the eighth week, the colloidal-gold reaction runs practically with the globulin albumen content, persisting in some cases to the eighth week and beyond, but still occurring in dilutions of 1 to 40 to 1 to 160.

Eskuchen[12] mentions only a mild pleocytosis and a positive globulin reaction. Boyd mentions that the fluid pressure is generally definitely increased but may be normal. It is usually clear, but may be cloudy. The cells vary with the stage of the disease, the count being high in the earliest stages and consisting of polymorphonuclears and lymphocytes in varying proportions. He states that the polymorphonuclear high percentages occur in the earlier stages. In the prodromal stage, Peabody found the lowest cell count to be 34 and the highest 1980. The cell count rapidly falls as the disease progresses and the polymorphonuclears are replaced by lymphocytes. Globulin was increased in a ratio inversely proportionate to the cells; slight in early stages and increasing as the disease progressed. The maximum globulin content was found in the third

and fourth weeks but was never excessive. Neal[17] reported a true hemorrhage and Froin's syndrome in 2 cases. Boyd[13] stresses the sugar estimation as being of great importance in differential diagnosis. The fluids of poliomyelitic patients gave a well marked Fehling reduction, while other diseases with which poliomyelitis might be confused showed a decrease in sugar content. The colloidal-gold reaction was very constantly a luetic curve. The reaction was most marked in the first week and after the fourth week was diminished or had disappeared.

Levinson[22] stated that the fluid might be normal in every respect after the preparalytic stage. He found the amount increased by 20 to 50 cc., the pressure increased by 300 to 700 mm. of water and the colloidal-gold reaction either showing no curve or else a change in the luetic zone. He found also, that the cells were in greatest numbers during the first week after the onset of paralysis. The majority of cells were lymphocytes (60 to 90 per cent) except in the early stages where polymorphonuclears predominated.

A review of hospital records in both acute and chronic poliomyelitis differs in no respect from the above.

Epilepsy. Mestrezat[14] states that the majority of fluids are normal in idiopathic epilepsy. There may be a slight increase in albumen and sugar. Lochelongue[34] reported the fluids normal in epilepsy and the cell count within normal limits.

Eskuchen[12] noted that in the majority of cases of idiopathic epilepsy the fluid was unchanged except that the pressure was elevated during an attack. He states that the globulin may be increased and that there is seldom a pleocytosis.

Levinson[22] made the same observations concerning increase of pressure during an attack. He also believes there is an increase in the amount of fluid during an attack but that there may or may not be an increase in the intervals.

Donath[35] found chlorin in crystals and by chemical tests in 18 out of 21 cases of idiopathic epilepsy. This observation has not been corroborated by others, the investigation apparently not having been undertaken.

One hundred hospital case records and statistics compiled by Tucker showed as follows: (1) Fluid always clear. (2) Pressures (reported in 36 cases) normal to slightly increased. (3) Cells consistently within normal limits. (4) Globulin negative to slightly increased. (5) Wassermann reaction negative (those showing a positive reaction were excluded). (6) The gold solution curve negative or showing a slight reduction (in 9 fluids).

Arteriosclerosis. In generalized cerebral arteriosclerosis without focal disease, the fluid is practically unchanged according to Eskuchen.[12] There may be a slightly positive globulin reaction and a mild pleocytosis. With encephalomalacia, pleocytosis and globular increase are frequent findings.

A study of many hospital case records reveals a distinct difference in the fluid findings of uncomplicated cerebral arteriosclerosis and in hemorrhage, thrombosis and embolism. In arteriosclerosis there were found no changes in pressure, color, number of cells, sugar or colloidal-gold reactions. In hemorrhage, the cellular elements were naturally increased in many cases because of the presence of blood, but in those cases in which the fluid was clear, about 33 per cent showed a moderate pleocytosis, with the majority of cells of the lymphocytic type. Occasionally large mononuclears were found and rarely a small number of polymorphonuclears. In one-half the cases, sugar was definitely though not markedly increased. Other findings were normal. In embolism and thrombosis, the sugar content was mainly affected. Here high percentages were found. Alpers, Campbell and Prentiss[23] have reported similar observations.

Amyotrophic Lateral Sclerosis. Mestrezat[14] studied the fluids in 2 cases of amyotrophic lateral sclerosis and in 1 case found the albumen and chlorid content normal, but the sugar very much increased. In the other case there was a slight hyperalbuminosis and a mild leukocytosis. Eskuchen[12] found a mildly positive globulin reaction, and the other contents normal.

Hospital case records show no changes of any character, so far as the ordinary routine examinations of the spinal fluid are recorded. No apparent independent and thorough investigations have been carried out in this disease.

Syringomyelia. In 1 case of syringomyelia studied by Mestrezat[14] an increase in albumen and sugar was found, all other findings being normal. Eskuchen[12] and Sicard[11] record all findings normal. Boyd[13] quoting Kaplan stated that there may be a marked protein increase without pleocytosis. He mentioned 1 case with a xanthochromia. In 4 other cases the fluids were normal.

In several hospital case records, the fluids were found clear, cells normal, globulin absent except in 1 case, sugar content slightly increased in 33 per cent, and the gold solution negative.

Cerebral Tumors. Lochelongue[34] stated that in cerebral tumors, the fluid pressure was usually increased, the albumin content normal, sugar increased, at times a moderate lymphocytosis and the chlorids normal or nearly so. Boyd[13] reported that the pressure was sometimes enormously increased and usually definitely increased. The cell count as a rule was normal but might be increased. The protein content as a rule was not increased, but more likely to be so if the tumor was a gumma. Rehm is reported by Boyd as recording the presence of cholesterin crystals and fat in cholesteatoma of the base of the skull. Boyd found cholesterin ester crystals in a tumor of the optic chasm.

Alpers[36] reports a study of 102 ventricular fluids in cases of tumor of the brain, with particular reference to the Lange gold test. In

his cases, the cells were increased in 9 instances; between 7 and 20 in 7 fluids, 73 in 1 fluid and 375 in 1 fluid. The quantitative albumen was increased in 37 fluids, total proteins increased in 45 fluids and the colloidal gold reduced in 35 fluids. The gold solution curve, however, was not uniform and reductions did not take place at all frequently in the socalled "tumor zone." He states: "most of the cases showed a reduction in the luetic or tabetic zones."

Huntington's Chorea. Eskuchen[12] reports no characteristic changes.

Hospital records confirm Eskuchen's report.

Paralysis Agitans. Eskuchen[12] reports no characteristic changes in this disease. Hospital case records, however, have shown that there is a gold-solution reaction in a majority of cases. In 10 case reports, there was a reduction in 7 fluids. In all but 1 of these the reduction occurred in the middle tubes (0001121000) slight in most instances, but moderate in 2 fluids (0233454210). In every other respect the fluids resembles those found in arteriosclerosis.

Subacute Combined Degeneration. Boyd[13] examined 2 fluids in this condition and reports the globulin slightly increased. The cells and other constituents were normal. In his report, Kaplan is quoted giving a description of 3 cases with a marked globulin increase and no pleocytosis.

A study of hospital case reports shows a clear fluid, normal pressure and cellular content, globulin absent or slightly increased in a few cases (2.3 per cent), sugar quite variable, Wassermann negative, and the colloidal gold negative in 98.5 per cent. Those fluids showing a gold solution curve gave no uniform reduction.

Spastic Spinal Paralysis. This disease is not, strictly speaking, a clinical entity but usually a part of some process in which spasticity is a predominating feature. It therefore should show, insofar as cerebrospinal fluid determinations are concerned, a reaction consistent with the underlying condition. Eskuchen stated that the fluid is for the most part normal, though there is often a mild pleocytosis and a mildly positive globulin reaction. No pleocytosis was found in any of the hospital case records reviewed.

Spinal Muscular Atrophy. Eskuchen[12] found an increase in pressure of the spinal fluid, but otherwise no uniform changes. Mestrezat mentions a similar result.

Brain Abscess. Levinson[22] found that in early brain abscess the fluid was clear and under slightly increased pressure. The cells approximate 9 to 10 per c.mm. The globulin may be slightly increased. In later or terminal stages a localized meningitis may occur and in some cases the abscess may break into the subdural space and the fluid then becomes that of a pyogenic meningitis.

Boyd[13] states that the cerebrospinal fluid may be perfectly normal in brain abscess, especially if the lesion is deep seated. If the abscess communicates with the subarachnoid space, a purulent meningitis,

with characteristic findings, results. Even in deep-seated abscess, there may be an increase in cells and globulin.

The writer's personal observations and review of case records agrees with the above.

Tetanus. Nineteen spinal fluid reports only are available for consideration in tetanus. Complete examinations were not carried out in all cases, therefore, any conclusions must be considered as tentative. The pressure is recorded as increased in 1 case. The fluid was clear in 9 cases, cloudy in 5 cases and not recorded in 5 cases. The cells varied and are reported as normal in 2 cases, as consisting of 90 to 95 per cent polymorphonuclears in 4 cases, as mainly lymphocytes in 7 cases (and presumably in the 2 normal cases), and not recorded in 6 cases. In all but the 2 normal cases and 3 in which the numbers are not given, the cells are definitely increased.

The globulin reaction is reported in 18 cases, negative in 4, doubtful in 4, definitely increased in 5, moderately increased in 2 cases. The sugar showed a marked increase in all but 4 cases and 1 case was not reported. The colloidal-gold reaction was tested in 7 cases, 5 being practically negative and 2 showing moderate reductions in the third to seventh tubes.

Rabies. One spinal fluid report is available. This shows an opalescent fluid, 60 per cent polymorphonuclears and 40 per cent lymphocytes, albumin 2 +, globulin 2 + and sugar 3 +.

Degenerative Conditions. A number of congenital and degenerative diseases, and birth injuries are grouped. These include the mental deficiencies. tuberous sclerosis, Friedreich's ataxia, amaurotic idiocy, spina bifida, Thomsen's disease, Alzheimer's disease, progressive spinal muscular atrophy, bulbar paralysis and hydrocephalus.

Eskuchen found no fluid changes in bulbar paralysis, Alzheimer's disease, mental deficiency or Little's disease. In the latter condition Eskuchen quotes Holzman as finding increased pressure in 1 case and Plaut, Rehm and Schottmüller a lymphocytosis. In 1 hospital case I found both increased pressure and a pleocytosis but other findings were negative.

In 23 case records on hydrocephalus, the fluid changes are not typical in any way. Fluids were clear in all but 1 instance; cells were increased in 6 cases; but the globulin reaction was negative in 9, doubtful in 5 and increased in 8. Sugar was increased in 13 cases and not reported in 2. The Wassermann reaction was negative in all cases in which it was reported (50 per cent). The colloidal-gold curve is given in 8 cases, being negative in 4, showing a mild reduction in the first 5 to 6 tubes in 3 cases and a stronger reduction in the last 5 tubes in 1 case.

Friedreich's ataxia, dystonia musculorum deformans, tuberous sclerosis and Thomsen's disease showed normal findings throughout.

One case of spina bifida had 26 cells, but other findings negative.

The birth injury cases showed pleocytosis and increased sugar percentages, but otherwise normal findings.

The fluid in progressive spinal muscular atrophy is reported as negative in all respects.

Amaurotic idiocy (1 case) showed a very slight increase in cells and a luetic curve.

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Foot Note.—Cerebrospinal Fluid Reports received from various New York City Hospitals and Clinics, from hospital studies made by Beverley R. Tucker, Richmond, Va., and from the Philadelphia General Hospital, The Orthopedic Hospital and Infirmary for Nervous Diseases and the Polyclinic Hospital of Philadelphia.

THE ELECTROCARDIOGRAM IN MYXEDEMA.

By Catharine Thacher,

and

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boston.

(From the Cardiographic Laboratory of the Massachusetts General Hospital.)

In 1918 White and Aub[1] published a series of 21 cases of hyperthyroidism and 2 of hypothyroidism comparing the parallelism between the metabolic rate and the amplitude of the *T* wave in the electrocardiogram. In the cases of hyperthyroidism they found a very limited parallelism between the height of the *T* wave and the percentage increase of the basal metabolism over the normal; but in the 2 hypothyroid cases, one, a patient with myxedema, and the other a Cretin, the amplitude of the *T* wave was below normal and increased after the administration of thyroid gland.

Since then electrocardiograms of 14 other cases of myxedema have been obtained at the Massachusetts General Hospital. Basal metabolic rates have also been determined before receiving any treatment, and subsequent electrocardiograms and metabolic rates were obtained on 10 of these cases after treatment. In the first electrocardiogram in every case there was a decrease in the height of the *T* wave in Lead II below normal, the highest reading being +1 mm., whereas the *T* wave in Lead II should normally have an upright deflection of 2 mm. or more. Each millimeter equals one ten-thousandth of a volt. The pulse rate averaged 68, the *P* wave was present in every case, there was no auriculoventricular or intraventricular block, and no definitely abnormal axis deviation was found. The *P–R* interval was less than 0.18 second, except in 1 case where it was 0.20 second. The *Q–R–S* complex in some instances was decreased in amplitude, approaching the "low potential" type and increased as did the *T* wave with thyroid treatment.

Zondek[2, 3] has reported increase in the size of the heart as studied by the Roentgen ray in myxedema and absence of both *P* and *T* waves in the electrocardiogram, the heart size decreasing, except for some widening of the aorta, and the *P* and *T* waves appearing after thyroid administration. He has also reported the same signs in a patient in whom symptoms of myxedema had gradually developed following a wound of the neck with suppuration of the thyroid gland.

ELECTROCARDIOGRAPHIC DATA AND BASAL METABOLIC RATE IN CASES OF MYXEDEMA.

No.	Sex.	Age.	Date.	Electrocardiogram.				Rate.	*P–R* interval in seconds.	Basal metabolic rates, per cent.	Treatment.
				Amplitude in millimeters. Each millimeter = 10^{-4} volt.							
				Lead.	*P.*	*T.*	*Q–R–S.*				
1	F.	54	Nov. 27, 1914	I	Flat	+0.5	+3	66	0.17	−20	Started Dec. 1, 1914; thyroid grs. iss t.i.d.
				II	+1.0	−0.5+1	+7				
				III	+1.0	−0.2	+7				
2	M.	29	Sept. 19, 1919	I	+0.5	+1.0	+3	65	0.16	−28	Had been taking thyroid off and on. Sept. 22, 1919, started grs. v daily.
				II	+2.0	+1.0	+8 −2				
				III	+1.0	Flat	+5 −2				
			Dec. 3, 1921	I	+1.0	+4.0	+6	80	0.14	+9	
				II	+2.0	+4.0	+16 −2			Dec. 19, 1921	
				III	+0.5	Flat	+10 −4				
3	F.	34	Feb. 23, 1921	I	+0.5	+1.5	+12	80	0.18	−28	Thyroid started Feb. 25, 1921.
				II	+1.0	+0.5	+11				
				III	+1.0	−1.0					
			Mar. 4, 1921	I	+1.0	+2.5	+18	80	0.16	−11	
				II	+1.0	+2.0	+18				
				III	+0.5	−1.0	+4				
			Mar. 12, 1921	I	+0.5	+2.5	+12	90	0.17	+3	
				II	+1.0	+3.0	+19				
				III	+0.5	Flat	+7 −2				
			Mar. 26, 1921	I	+0.5	+3.0	+11	80	0.15	+1	
				II	+1.0	+4.0	+21				
				III	not done.						
			April 23, 1921	I	+0.5	+3.0	+11	60	0.16	+1	
				II	+1.0	+3.0	+22 −5				
				III	+0.5	Flat	+5 −3				
4	M.	30	May 16, 1921	I	+0.5	Flat	+5	56	0.18	−20	Hyperthyroid Oct., 1915, B. M. R. +78; 6 Roentgen-ray treatments. Thyroid grs. ivss daily, started May 16, 1921.
				II	+1.5	+1.0	+6				
				III	+1.0	+1.0	+2				
			June 1, 1921	I	+0.5	+1.0	+5	68	0.16	−8	
				II	+1.5	+2.5	+9				
				III	+1.0	+1.5	+4				
			June 13, 1921	I	+1.0	+2.0	+6	70	0.16	−13	
				II	+2.0	+2.0	+12				
				III	+1.0	Flat	+6				
			Sept. 19, 1921	I	+0.5	+2.0	+5	56	0.17	−1	
				II	+2.0	+2.0	+11				
				III	+1.0	+1.0	+5				

			Jan. 4, 1922	I	+1.5	+4.0	+9	75	0.15	+2	
				II	+3.0	+4.0	+15				
				III	+2.0	+1.0	+9				
5	F.	..	Aug. 22, 1921	I	Flat	Flat	+6	50	0.15	−35	
				II	+1.0	Flat	+4 −2	auricular			
				III	Flat	Flat	−4	premature			
								beats.			
			Oct. 31, 1921	I	Flat	Flat	+2	70	0.15	−13	
				II	+0.5	−1.0	+2 −6				
				III	+0.5	−1.0	+2 −7				
6	F.	53	Jan. 23, 1921	I	+0.5	Flat	+6	80	0.16	−27	Thyroid grs. iss b.i.d., started Jan. 22, 1921.
				II	+1.5	Flat	+5				
				III	+1.0	Flat	+1				
			May 2, 1921	I	+1.0	+1.0	+8	80	0.15	−8	
				II	+2.0	+2.0	+10 −2				
				III	+1.0	+0.5	+1 −4				
			Nov. 9, 1921	I	+1.0	+3.0	+12	75	0.17	−18	
				II	+2.0	+3.0	+9 −3				
				III	+1.0	Flat	+2 −7				
			April 24, 1925	I	+1.0	+4.0	+15	80	0.17		
				II	+3.0	+5.0	+10 −3				
				III	+2.0	+1.0	+1 −5				
7	M.	56	June 14, 1921	I	+0.5	−0.5	+7 −3	75	0.18	−33	Thyroid grs. vi daily, started June 14, 1921.
				II	+0.5	+0.5	−3				
				III	+0.5	+0.5	−6				
			Sept. 21, 1921	I	Flat	Flat	+4 −3	100	0.19	−19	
				II	+1.0	Flat	−3				
				III	Flat	+1.0	+2 −10				
			Nov. 21, 1921	I	+1.0	+2.5	+15 −5	80	0.17	−18	
				II	+1.0	+1.0	+3 −4				
				III	+1.0	−1.0	+2 −12				
			Dec. 19, 1921	I	+0.5	+2.5	+15 −2	95	0.16	−8	
				II	+1.0	+1.0	+3 −4				
				III	+0.5	−1.5	+2 −13				
8	F.	53	Jan. 24, 1923	I	Flat	Flat	+4 −2	70	0.19	−34	Thyroid grs. v b.i.d., started Jan. 27, 1923.
				II	+0.5	Flat	+2				
				III	Flat	Flat	−3 +2				
			Jan. 29, 1923	I	Flat	−1.0	+7	86	0.19	−25	
				II	+1.0	Flat	+3				
				III	+0.5	+1.0	−2 +2				
			Feb. 6, 1923	I	+0.5	+1.0	+7	100	0.18	−18	
				II	+0.5	+1.0	+5				
				III	+0.5	+0.5	+3				
			Feb. 13, 1923	I	+0.5	+1.0	+9	90	0.17	−12	
				II	+0.5	+1.0	+10				
				III	+0.5	+0.5	−3				

ELECTROCARDIOGRAPHIC DATA AND BASAL METABOLIC RATE IN CASES OF MYXEDEMA.—(*Continued.*)

No.	Sex.	Age.	Date.	Electrocardiogram.				Rate.	*P–R* interval in seconds.	Basal metabolic rates, per cent.	Treatment.
				Amplitude in millimeters. Each millimeter = 10^{-4} volt.							
				Lead.	*P.*	*T.*	*Q–R–S.*				
			Feb. 27, 1923	I	+1.0	+1.5	+8	85	0.15	+2	
				II	+0.5	+2.0	+6				
				III	−0.5	+1.0	Flat				
			April 10, 1925	I	+0.5	+2.0	+8	64	0.16	−4	On thyroid grs. iii daily.
				II	+1.0	+3.0	+10				
				III	+0.5	Flat	−4				
9	F.	44	Jan. 26, 1923	I	+1.0	−1+1	+4	80	0.15	−34	Thyroid grs. ix daily, started Jan. 26, 1923.
				II	+1.5	−1.0	+8				
				III	+1.0	−1.0	+6				
			Jan. 29, 1923	I	+1.0	+1.0	+5	88	0.16	−20	
				II	+1.5	−1.0	+8				
				III	+0.5	−1.0	+3				
			Feb. 3, 1923	I	+1.0	+2.0	+7	100	0.17	−12	
				II	+1.0	+2.5	+13				
				III	+0.5	Flat	+7				
			Feb. 12, 1923	I	+1.5	−1+2	+13	130	0.14	−4	Died Feb. 28, 1923.
				II	+1.5	+2.0	+13				
				III	+1.5	+3.0	+11				
10	M.	47	April 4, 1924	I	+0.5	Flat	+3	80	0.16	−18	Thyroid started March 29, 1924.
				II	+1.0	Flat	+7 −2				
				III	+0.5	Flat	+2				
11	F.	42	April 23, 1924	I	Flat	−0.5	+9	70	0.14	−37	Thyroid grs. viiss daily, started April 22, 1924.
				II	+1.0	Flat	+9				
				III	+0.5	+0.5	+1				
			May 3, 1924	I	+0.5	+1.5	+12	90	0.16	−8	
				II	+2.0	+2.5	+17				
				III	+1.5	+0.5	+6				
			Mar. 13, 1925	I	+0.5	+1.0	+9	60	0.16	−27	Taking gr. i daily past six months, started grs. vi daily March 13, 1925.
				II	+2.0	+1.5	+9				
				III	+1.0	+1.0	+2				
			Mar. 27, 1925	I	+0.5	+2.0	+9	90	0.16	−7	
				II	+3.0	+4.0	+13				
				III	+2.5	+1.0	+4				
12	F.	24	Dec. 11, 1923	I	+1.0	+3.0	+8 −2	70	0.19	−32	Thyroid grs. xx, started Dec. 16, 1923.
				II	+1.5	Flat	+20				
				III	+0.5	−2.0	−2+19				

			Dec. 17, 1923	I	+0.5	+3.0	+7 −3	65	0.19	−16	
				II	+1.0	+1.0	+20				
				III	+0.5	−2.0	−2 +17				
			Dec. 22, 1923	I	+1.0	+2.0	+9 −2	110	0.18	+3	
				II	+2.0	−1.0	+20				
				III	+1.5	−3.0	−2 +20				
			Dec. 24, 1923	I	+1.0	+2.5	+10 −2	90	0.2	+11	
				II	+2.0	+2.0	+23				
				III	+1.0	−1.0	−3 +19				
			Jan. 9, 1924	I	+1.0	+3.0	+9 −2	80	0.18	−7	
				II	+2.0	+4.0	+22				
				III	+1.0	Flat	−2 +17				
			Feb. 29, 1924	I	+1.0	+3.5	+10	80	0.17	+8	On grs. iv daily; stopped thyroid July, 1924.
				II	+1.5	+4.0	+20+				
				III	+1.0	Flat	−2 +13				
										−42	Started March 20, 1925 on grs. iss t.i.d.
			Mar. 27, 1925	I	+0.5	+3.0	+8 −1	54	0.18	−28	
				II	+1.0	+2.0	+19				
				III	+0.5	−1.0	−2 +15				
			April 25, 1925	I	+1.0	+4.0	+13	75	0.18	−2	
				II	+1.5	+3.0	+22				
				III	+0.5	−1.0	+12				
13	F.	41	Feb. 27, 1925	I	Flat	Flat	+4 −3	60	0.17	−28	Thyroid grs. iv daily.
				II	+0.5	−1.0	+6 −3	auricular			
				III	+1.0	Flat	+7	premature			
								beats.			
			April 28, 1925	I	+0.5	−1.0	+5	75	0.18	−6	
				II	+1.5	−1+1	+10 −3	auricular			
				III	+1.5	Flat	+8	premature			
								beats.			
14	F.	38	April 10, 1925	I	+1.0	+0.5	+3 −3	90	0.18	−24	Thyroid started April 22, 1925, grs. ix daily.
				II	+1.0	Flat	−2				
				III	Flat	Flat	−2 +2				
			April 28, 1925	I	+1.5	Flat	+3 −3	100	0.18	−18	April 28th, grs. vi daily.
				II	+1.0	Flat	+2				
				III	Flat	+0.5	−3 +3				
			May 7, 1925	I	+1.0	Flat	+5	75	0.17	−15	
				II	+2.0	+1.5	+4				
				III	+1.0	+1.0	−4 +4				

Fahr[4] has recently reported cardiac dilatation in 4 cases of myxedema with marked diminution in size after treatment. Also the electrocardiogram showed diminution of the amplitude of the T wave which became higher after medication. However Willius and Haines,[5] in a study of 162 cases of myxedema, failed to find any appreciable dilatation in most of the cases although they did obtain abnormal electrocardiograms.

One of us[6] has recently reported the study of the electrocardiogram in cretinism, another type of hypothyroidism. In all of the 8 cases examined the T wave in Lead II was below normal. In the 3 cases who were examined again after thyroid administration the T waves had increased in amplitude and the Q–R–S waves also showed higher potential difference.

Summary. Our 14 cases of myxedema (see table) showed consistently a low T wave in Lead II before treatment with increase in positive amplitude after treatment. Thus there is a distinct parallelism between the T wave of the electrocardiogram and the basal metabolic rate in hypothyroidism (Figs. 1 and 2).

In addition, there is a general decrease in potential of all electrocardiographic deflections in all leads in myxedema, with increase after treatment. This same so-called "low potential" in all leads is found in one other condition, that of myocardial exhaustion due to serious coronary sclerosis. This fact is evidence that the heart action is sluggish during myxedema in accord with the recent finding of Einthoven that the electrical and mechanical expressions of muscular activity are not only synchronous but also tend to be parallel in degree. The T wave in Lead II may also be lowered by digitalis; but the "digitalis T" is somewhat different from the "myxedema T" or the "myocardial weakness T," the deflection being more often diphasic, particularly with the S–T interval inverted.

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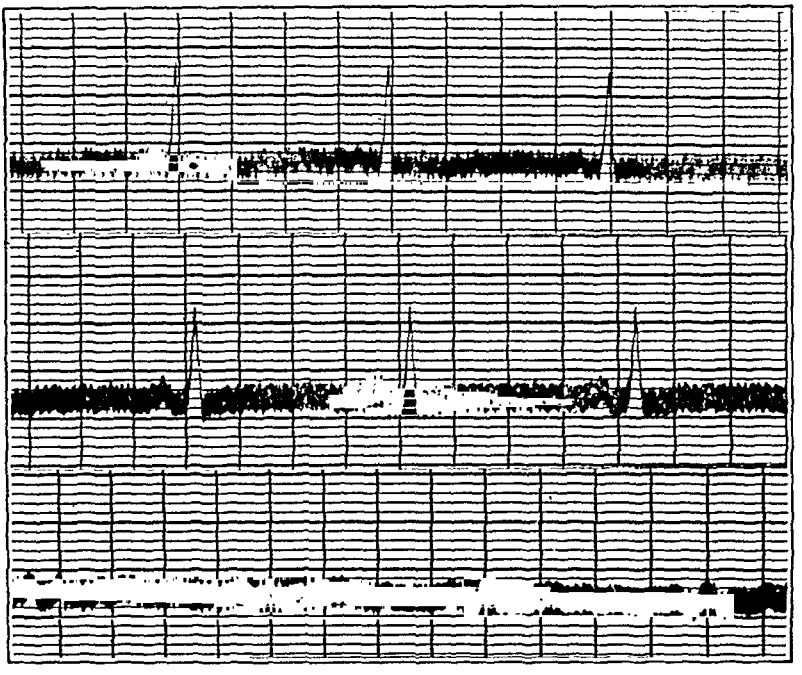


FIG. 1.—Electrocardiogram (Leads I, II and III) of Case 11, on April 23, 1924, when basal metabolic rate was −37. Note low amplitude of the *T* wave, and also of the *P* wave in all leads. (See Table.) Time interval = 0.2 second. Potential difference: 1 mm. = 10^{-4} volt.

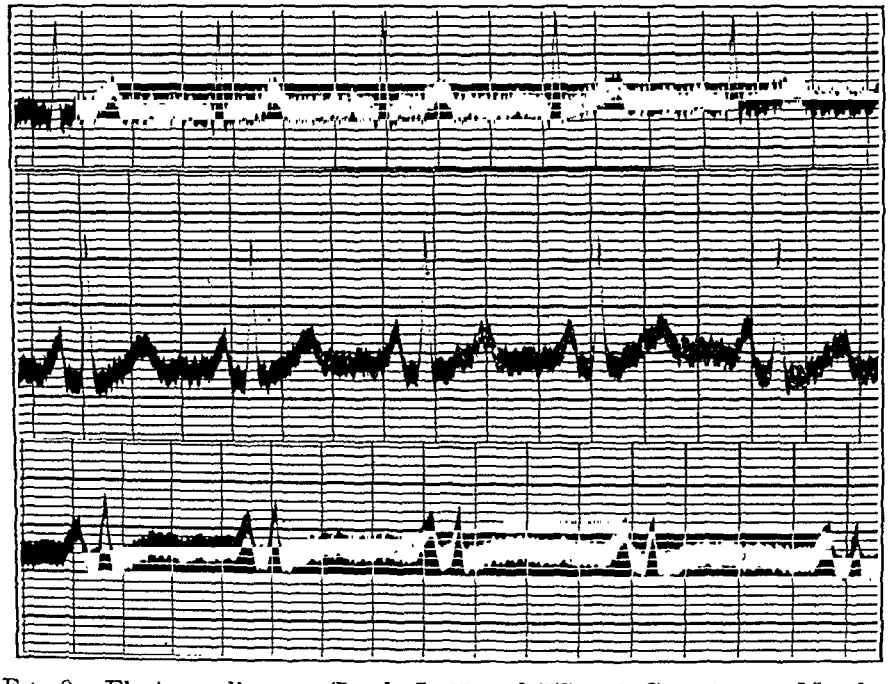


FIG. 2.—Electrocardiogram (Leads I, II and III) of Case 11, on March 27, 1925, when basal metabolic rate was −7. Note increase in amplitude of the *T* and *P* waves in all leads and of *R* in Leads II and III. (See Table.) Time interval = 0.2 second. Potential difference: 1 mm. = 10^{-4} volt.

MEGACOLON: A RESUMÉ OF THE LITERATURE AND REPORT OF A CASE. RAMISECTION PROPOSED AS A FORM OF TREATMENT.*

By Henry J. Bartle, M.D.,
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Literature. The monograph by Finney[1] is the most complete of the many references that I have consulted in my work of studying the literature of this obscure condition. He cites the reports of Parry, in 1825, although Barrington-Ward,[17] in quoting Jayle, says that Runyon in the seventeenth century reported a typical case in a girl aged five years. Billard, in 1829, reported a case in a child, aged six days, in which the lower part of the small, and all of the large, bowel were thickened and sclerosed. These were followed by Ebers, in 1836, and in 1842 von Ammon reported 2 cases—one, a child who died shortly after birth, and another, a fetus at about the seventh month. After these came other cases, reported by Oulmont, in 1843, Banks, Bunfer and Favalli, in 1846, Little and Galloway, in 1850, Gay, in 1854, Henock, in 1861, and in America by Lewitt, in 1867, and Jacobi, in 1870. Then come Barth, Peacock, Gee, Brostow, Morris Fütterer, Middeldorf, Cheadle, Gauma and others.

It is only fair that here attention be called specifically to the report made on May 27, 1886, by a prominent Philadelphia clinician who is still living—Dr. William E. Hughes[2]—which was published in 1887, before Hirschsprung produced his monograph describing this malady which bears his name. Hughes reported the autopsy findings in a boy, aged three years, dying during an attack of acute colitis. The colon had a capacity of 14 pints (7000 cc.) The gut wall was hypertrophied, and the dilatation while present throughout the colon was marked in the sigmoid region where a diameter of 4 inches was noted.

In 1888 Hirschsprung[3] published his monograph which bears the date of 1886 as the time of writing. He reported 2 cases which during life presented symptoms of constipation and meteorism without signs of stenosis of the gut tract. The first case died at eleven months of progressive cachexia, and the second case died at seven months of multiple ulcerations of the colon. Each case exhibited dilatation of the colon with hypertrophy of the bowel wall. Later 2 more cases were added, making 4 in all.

The case reported by Formad,[4] in 1891, is of interest because it is frequently referred to in the literature and because of the extreme size of the colon, also because of the age, twenty-nine years, to

* Read before the American Gastroenterological Association, at the Annual Meeting in Atlantic City, N. J., May 25, 1925.

which the patient survived with such a gross deformity. Formad stated the size of this man's colon was that of a cow's, and after removal of its 40 pounds' of contents the weight of the colon was a little under 7 pounds. The rectum was normal and the greatest dilatation was found in the sigmoid, although the whole colon was enlarged even to the cecum, which was the least enlarged of all portions. Throughout the whole extent of the colon the wall was found hypertrophied, but there was an anomalous arrangement of the circular and longitudinal musculature and the longitudinal bands were absent. The skeletal muscles were atrophied, and there was complete absence of all fatty tissue even to the omentum. Death occurred suddenly while the man was attempting to defecate. The exact cause of death was not stated by Formad.

Genersich, Demme, Walker and Griffith later reported similar cases, and when Mya,[5] in 1894, added 2 cases, his review of the literature showed a total of 9 cases, although actually there were more cases on record at that date. One of Mya's cases which died during an attack of acute enterocolitis, exhibited ulceration of Peyer's patches.

Formad refers to a few interesting cases. Gruber reported a sigmoid 4 or 5 inches in diameter. Little and Galloway reported a case in which the transverse colon had a diameter of 6 inches and the sigmoid varied from 12 to 20 inches in diameter. Peacock's case had a colon capacity of 15 quarts, and the sigmoid varied from 6 to 8 inches in diameter. Cruveilhier reported a case with the colon the size of a horse's great gut, and one with a diameter of 14 inches.

In 1893 Osler[6] reported 2 cases of marked constipation without fecal impaction or rectal or anal obstruction. He takes pains to remark, however, that Dr. Halstead, who examined 1 of these cases, thought that the sphincter was tight, although Osler himself did not agree to this. Marfan, Treves, Concetti, Fenwick, Fritz, Richardson, Eserich, Frommer, Duval, Kredel, Cheinisse, Perthes, Bing, Pfisterer, Danzinger, Löwenstein, Ito and Sayesima followed with case reports, so that a total of 206 cases was found in January, 1908, when B. W. A. Fisher and Finney[1] made their exhaustive review of the literature.

In the interval of the following seventeen years many cases have been collected, so that the literature of today is quite profusely supplied with reported cases, and with statistical reports on the results of treatment by either the medical or the surgical avenues of approach.

Reference may be made, for instance, to Hubbard,[7] L. W. Johnson,[8] P. P. Johnson,[9] Beath,[10] Matthews,[11] Rogers,[12] Drueck,[13] Shaine[14] and Porter.[15] Neugebauer[16] reported a series of 169 cases in 74 of which the sigmoid alone was involved. Barrington-Ward[17]

did necropsies on 19 cases and found the rectum involved in a few of them. Duval[18] studied 59 cases. Löwenstein[19] reports 44 surgical cases and 59 medically treated cases; Terry[20] reports 110 surgically treated cases. It is to be understood that these cases may overlap, in a measure, for each man has collected the cases, many of which had already played a part in previous statistical studies. However, the cases reported are many when taken in the aggregate. The nearest estimate to the incidence of this condition is that given by Fenwick,[21] who, in a review of 30,000 necropsies in the London Hospital for Sick Children, found only 3 cases—1 case in every 10,000.

Etiology. Many theories have been advanced to explain the etiology of this condition developing in the first year of life, or even during the baby's intrauterine life. A survey of the following list of causes advanced by Barrington-Ward[17] and quoted by Drueck,[13] Bassler,[22] Finney[1] and others reveals the fact that practically every embryonal, histologic, pathologic and physiologic field has been scanned in an endeavor to find the answer and so point to a definite plan of treatment.

THE LIST OF CAUSES. 1. *Mechanical.* Torsion of the sigmoid, because of extreme mobilization as the result of too long mesosigmoid, or because of too great length of the tube itself, or actual blocking of the fecal current from atresia of the anal canal, rectum or sigmoid; imperforate anus (partial type); hypertrophied rectal valves; overdevelopment of O'Beirne's sphincter; the drag of a sigmoid overloaded with meconium acting as a valve, thus preventing its own emptying.

2. *Neuropathic.* Neuromuscular defect, or even a paralysis of a segment of gut; lesion of the sympathetic system; reflex spasm of sphincters due to anal fissure.

3. *Inflammatory.* Chronic colitis leading to changes in the physiology and anatomy of the gut tube through bacterial, chemical and toxic factors.

4. *Congenital.* Anomalous development, that is, congenital dilatation and hypertrophy, as suggested by Hirschsprung.[3] It has been suggested, too, that either of these may be the true congenital anomaly, and the other the secondary result of the primary defect.

To say that a pathologic condition is congenital explains nothing; therefore, I have sought for an explanation of how this hypertrophy and dilatation could be brought about. So, not included in this list, there is another which may be worth considering, and that is a developmental cause. While the embryo is developing its great gut, at the time when by the rapid downward growth of the liver resulting in a marked disproportion between the size of liver and the cavity of the abdomen, a portion of the small gut and all of the large gut is pushed out of the abdomen into the sac. When more nearly normal relations between the size of liver and that

of the abdominal cavity begin to be reëstablished the gut recedes within the peritoneal space, and through growth of the great bowel upward from the sigmoid and rectum, the descending colon, then the transverse, and finally the ascending portions of the great gut take up the positions in which they are found at birth or soon after, and become fixed; in so doing the complete twist from left to right is given to the mesentery of the small bowel as the stomach turns its left side forward. Therefore if there be an anomalous development accounting for this condition of megacolon I think it extremely likely that the condition begins in the very early developmental stage of the embryo—that is, during the first few weeks after gestation. It is just possible, through this displacement and torsion to which the gut with its mesentery is subjected, that the innervation is in some way interfered with, and that the proper balance or reciprocal relationship of the two motor nervous supplies of the gut (the sympathetic and the parasympathetic) is not maintained, and, as a result, function of the colon would be impaired early in intrauterine life.

Pathology. Roughly, 33 per cent of the cases show involvement of the colon in its sigmoid portion alone. A few cases have shown the whole colon to be involved, and rarely the cecum and rectum are enlarged. Many of the surgeons note the lack of development of the external coat of longitudinal fibers which in the normal colon constitutes the longitudinal bands of the great gut. These bands may be absent or poorly defined. The middle coat of circular fibers is usually either well developed or overdeveloped, contrary to what one would expect to find in a dilated colon. The inner coat of muscular tissue may be of normal thickness, as may the mucosa, but this latter usually shows signs of chronic inflammatory changes, such as hypertrophy of its various layers or focal necrosis from minute fissures up to large ulcerated areas, which may extend down through the muscular layers and penetrate the serosa. The serosa is usually blanched when the abdomen is opened if there be a great amount of feces within the colon, due to the pressure on the mesenteric vessels, which are usually long and tortuous, as they lie within the two layers of the mesocolon. The lymph glands are usually hard and may be cystic, and a chronic lymphangitis is frequently evidenced by the thickened mesocolon.

The sigmoid may have a diameter many times its normal size, and the whole colon be greatly lengthened so that it folds and refolds upon itself, sometimes filling the pelvic and greater part of the abdomen and thus crowding the small intestines up under the liver, stomach and spleen.

Symptoms. For every female afflicted with megacolon there are 3 males similarly afflicted. Many of the cases are diagnosed soon after birth, and by far the largest proportion of them before the first year.

The only constant symptoms or signs are: (1) A history of constipation with constant laxative, purgative or enema habit, dating very likely from birth. (2) Abdominal distention. (3) Roentgen-ray findings after a barium enema.

Besides these three cardinal ones there is a mixed array of signs and symptoms which may be present singly or in combination: (1) Muscle atrophy, especially of the abdominal wall, allowing the loops and coils of the bowel, undergoing their peristaltic activity, to be seen; weakness of muscles of extremities. (2) Loss of the subcutaneous fat. (3) Toxic symptoms—headaches, socalled bilious attacks, nausea, vomiting, chilliness, prostration, stupor and lassitude, and irregular fever. (4) Anemia is rather rare, except in the far-advanced cases. (5) Lack of proper development. (6) Because of the impaired mechanics of the gut tube, sleep is apt to be disturbed, and during the day the child is restless, irritable and unhappy. (7) Usually the child will not even try to defecate when placed on the vessel, but "will sit for hours;" the stool in response to enema may be formed and only thumb sized; indeed, not the large massive balls or sausages that one would be led to expect from some textbook descriptions. (8) Palpation may elicit a large mass in the left lower quadrant, but if the mother has been giving good attention to the child, the bowel may be found relatively empty; it is not necessary to have fecal impaction in megacolon; but always the bowel is distended with gas and is easily compressible without resulting pain. (9) There has been little attention paid to the tonicity of the anus in the reported cases, but when this finding has been recorded a spastic state or hypertonicity would seem to be the rule. It is quite likely that hypertonicity will be found more frequently if looked for during life. Finney states that the anus is usually normal, but I believe this observation relates to the examination of the dead sphincter, so naturally a functional disturbance would not be found.

Treatment. Hubbard[7] gives a good statistical review of the comparisons to be made between treatment given by the medical and the surgical methods. Duval[18] showed that the mortality in those cases treated medically is 74 per cent, and in those treated surgically 34 per cent. Löwenstein[19] has worked out two sets of statistics. He first reported 44 operative cases, of which 21 (48 per cent) died, 2 were unimproved, 7 were improved and 15 (34 per cent) were cured. Of 59 cases treated medically, 39 (66 per cent) died, 9 were improved, 4 were unimproved and 7 (12 per cent) were cured. Finney,[1] in commenting on these figures, concludes that the surgical mortality rate is two-thirds that of the medical, and that the surgical recovery rate is three times as great as the medical. Terry[20] collected 110 surgically treated cases, and records that there were 82 (74 per cent) recoveries and 28 (26 per cent) deaths. Neugebauer[16] collected 133 medically treated cases,

and reported cures in less than 2 per cent. He states that in selected cases the two-stage operation (anastomosis and, later, resection) has given as high as 90 per cent recoveries.

So the statistical evidence is plainly against the expectant medical plan of treatment, yet one must remember that it is just possible that many of the surgically treated patients may have died of various causes since their discharge marked "cured" was written; while all medical cases may have been scored up against "death from megacolon," even though these deaths occurred later from intercurrent disease. Even though these statistics may be misleading, I believe that in the majority of cases treatment eventually will have to be of a surgical type. It is hard to bring one's self to condemn these little patients to the vicious colon resection operation while there is the slightest possibility of helping them in some other way, and that is one reason why I am proposing ramisection as outlined under "Theoretical Discussion" of this paper.

In a medical way I believe the best results are to be obtained through the judicious use of sine-wave electricity to the abdomen and by preventing the possibility of toxemia from intestinal decomposition by the removal from the diet of all food containing animal protein, excepting milk and its products, such as cheese and butter; but even milk may have to be withdrawn if it be found that it disagree. Bacillus acidophilus and lactose should be given, watching the effect of the latter in producing distention through fermentation. The starches are almost universally condemned by most clinicians, but I believe they are usually well borne, even when given in excess for the purpose of building up the caloric requirements of the diet after the withdrawal of the animal protein—the chief offender through decomposition in the torpid great gut.

Laxatives must be given to procure some motility. Sodium sulphate in ½-dram doses, or less, night and morning, is probably the best because of its tonic action on the bowel musculature as contrasted with the relaxing effect of magnesium sulphate, which is not well borne. The mineral oils are bad because a lubricant is not called for in this condition, and because there is always the possibility of impairing the assimilation of food through its use. One cannot afford to take this risk in these patients for they are usually far below normal and must be built up through sufficient food intake, with olive oil and cod-liver oil, preferably fortified by the vitamins. Yeast is probably a poor form of medication in these cases because of the possibility of increasing the distention, which is sufficiently embarrassing to the patient's comfort under the best of conditions.

The wearing of an elastic binder, made to fit by careful measurement, is advisable; but, as a rule, it is a procedure difficult to follow out, because adjustments have to be made frequently to accord with the varying diurnal dimensions of the abdomen. All the usual

hygienic measures should be adopted to benefit the child generally. Exercise, especially, should be encouraged. Enemata should be given daily to aid in the emptying of the sigmoid. Normal salt solution is the best, but 5 to 10 per cent glucose, or 5 per cent sodium bicarbonate or sodium sulphate solutions may be used.

Lastly, medicines may play a very helpful part. Nux vomica is perhaps the most useful one for its stimulating effect on the vago-pelvic (bulbosacral or parasympathetic) nerve supply of the large gut, as well as for its tonic effect on the musculature. Adrenalin is contraindicated if our conception of an overactive sympathetic supply be correct. The use of pituitrin has been advised by Berger,[32] who reports good results from its administration in 10-drop doses four times a day, by mouth. Arsenic and iron (preferably one of the albuminoid forms) may be found extremely useful as reconstructives.

By these measures some of these sad little patients may be helped along sufficiently to make life a pleasure rather than a burden to them and their parents, and if, by following them, we do not effect a cure, we may have the satisfaction of knowing that at least we have made conditions better, and that the ability of the patient to withstand the serious and dangerous operation of resection—if that be the type of operation chosen—is greatly enhanced.

Case Report. G. L. C., 3d, male, aged three and a half years, was referred to me on April 17, 1923, by Dr. George T. Tracy, with a chief complaint of irregular bowel movements, abdominal distention and passing of flatus. The family history is negative, except for atonic constipation in the mother and the maternal grandmother. There are two younger sisters and one older brother, normal in every way except for hypertrophied tonsils.

Past Medical History. The child was born naturally; weighed a little over 8 pounds. At birth there were already erupted the two lower central incisors, which were immediately removed by the doctor in attendance. He was breast fed for six months, and then placed on modified milk. Almost from the day of his birth the bowel movements have not been normal. Laxatives, enemata and cathartics have been resorted to constantly since his first year to produce long, thin, cylindrical bowel movements. He has suffered none of the infections of childhood, but has had frequent socalled bilious attacks—bad color (sallow and pale) prostration and crossness. At all times he has been easily chilled by the slightest exposure, so that he actually feared the cold; he has had very little inclination toward exercise, and never cared to run about and play with the other children.

Ten months previously (July, 1922) a diagnosis of anal fissure, with very marked contraction of the sphincter, was made by

Dr. J. H. Allen. He made an uneventful and prompt recovery on local application of 2 per cent silver nitrate.

Present Illness. There had been no marked change from his previous condition, except that recently the child had suffered with more frequently recurring bilious attacks. The mother had noticed that the constipation was more pronounced, requiring a greater amount of laxative medicine and, occasionally, oil rectal injections because of the hardness (in consistency) of the fecal movements. The mother had noticed, too, that the distention of the abdomen had increased during the last six months, and was greater, especially after she had given the patient white bread and potatoes. Under the direction of Dr. Tracy the child's diet had been properly regulated, so that it was well balanced, and contained more than the usual amount of foods, insuring a sufficient cellulose residue. Much experimenting had been done in administering milk and its modifications with the usual diet, and in withholding it, without producing any change in the patient's symptoms.

Physical Examination. The boy weighed 32 pounds, and the mother felt that he had gained very little in weight, if any, within the past six or eight months. His skin was pale, but the mucous membranes were of a good red color, so that anemia was not striking, considering his blonde complexion. The scleræ were of the usual healthy pale blue color, and the pupillary reactions were normal. The nose and ears were negative. The tongue was clean and the tonsils, also, to compression testing. The usual number of teeth—twenty—had erupted. A space which should have been filled by the lower central incisors (which were removed immediately after birth) had not been encroached upon by the eruption of the lateral incisors, and this space caused a lisp in the child's articulate speech, which was otherwise normal, and seemed to denote that his mentality was up to the standard norm for his age. The heart and lungs and mediastinum were negative to the usual physical test procedures. There was no adenopathy, and the bony development was normal except for a suggestion of a Harrison's groove, because of the marked distention and protrusion of the abdomen.

The abdominal wall was very thin, and the recti abdominalis could not be pinched up between the examining fingers. The umbilicus protruded slightly. There was no hernia evident at the umbilicus, or inguinal rings, which was surprising considering the thinness of the abdominal wall, for loops and coils of the small intestine undergoing peristaltic movement were easily visible over the dome of the abdomen. Percussion gave deep tympany in both flanks and, to a less marked degree, across the upper abdomen. The abdomen could be easily compressed by the palpating hand, and no masses were felt, especially along the course of the descending colon and sigmoid.

The musculature of the extremities was underdeveloped, but was not wasted. There seemed to be more than the normal moderate degree of lordosis seen in children, but because of the abdominal protrusion this could not be accurately estimated. The umbilical reflex was absent, the cremasteric was doubtfully present and the patellars were normal.

Examination of the anus, while feared by the little patient —evidently because of his fairly recent proctologic experience— proved to be painless, but the anal muscle throughout its depth was tonically contracted, so that considerable force had to be exerted to intrude the anointed index finger tip within the anal canal. No linear induration could be palpated at the site of the former fissure, so that it did not seem possible that scar tissue formation could be a factor in producing the apparent overtonicity of the muscle. The anus was dragged easily to the posterior and to both lateral directions without the production of pain. The finger was introduced to its full length, and no feces was found within the rectum, nor were thickened rectal walls palpated, nor could a mass in the left lower quadrant be palpated bimanually. More relief was experienced, I imagine, by the examiner than by the patient on withdrawing the finger, for it was blanched by the constricting pressure of the hypertonic anal sphincter.

Since the purpose of this paper is to serve as a text, and to call to the attention of diagnosticians the possibility of the existence of megacolon without large colonic collections of feces, let me say that I did not call this a case of Hirschsprung's disease. The evidence did not seem sufficient to warrant such a diagnosis, nor was I willing to subject this patient to the danger of a colon resection, even though it was known that marked atony and dilatation of the colon existed. There was the marked atrophy of the abdominal musculature to be considered, for it was possible that this was one of the obscure types of congenital asthenia (amyotonia congenita). Then the tonically overactive anal sphincter could have explained the apparent constipation. It was thought wise to place the child on tonic treatment, to encourage the development of the abdominal muscles by exercise and massage, and to endeavor to procure some relaxation of the sphincter by the daily insertion of the finger to stretch and iron out the muscle; but little was hoped for from this procedure—as little as from the use of dilators where there is no scar-tissue deposit.

On the return of the patient in October, 1923, after the family's return from Maine, whence they had gone shortly after his first visit, I was shocked on observing his condition. He had gained only ½ pound (weight, 32½ pounds); he walked with a shuffling gait, sliding the feet along without lifting the toes, and so, frequently falling. He could walk up only two steps of the stairs

without a prolonged rest, and this was possible only when he threw his body forward and maintained his balance by placing his hands on his knees as he labored to step up. The lordosis was decidedly marked, and the angulæ scapulæ stood out and were of the alar type. The shoulders and pelvic muscular groups were markedly wasted, as were the palmar and thenar interossei. He could not climb up on the examining table from a stool, and, when aided, fell upon his face on the table top, his arms to the side, powerless to elevate his torso by his weakened shoulders and arm muscles. When placed upon his back he was unable to rise to a sitting posture even when allowed the use of his hands. The abdominal muscles were as thin as before, and the anus was still rigid. There had been no improvement in his bowel function.

He was seen by Dr. William G. Spiller, who ruled out muscular dystrophy and made a diagnosis of muscular atrophy concomitant with megacolon.

Dr. Spiller reported: "November 3, 1923: The boy moved all four limbs freely. It seems very doubtful to me whether he has atrophy of the shoulder girdle and interossei muscles. He does not have the 'loose shoulder' and 'winged scapulæ' so common in muscular dystrophy. His patellar reflexes also are very prompt, even probably a little exaggerated, which would be unusual in progressive muscular dystrophy. His biceps and triceps reflexes are not distinct on either side. He can rise from the floor without assistance, and has only a little tendency to 'climb on his thighs' to assist himself in elevating his trunk. The distention of the abdomen is remarkable, and when he stands he has some tendency to lordosis; this seems to me to be secondary to his distended and protruding abdomen. He has difficulty in going upstairs. His sensation for pinprick is good. It is difficult to test other forms of sensation in a child four years of age. Tonicity of limbs when they are moved passively seems good. The boy is weak everywhere but he has no local atrophies, and the weakness is such as could come from some systemic disturbance with malnutrition. The case does not appear to me as one of amyotonia congenita. If this case be one of progressive muscular dystrophy it is without characteristic findings and could only be in the early stage. It does not appear to me as one of muscular dystrophy. The condition is suggestive of megacolon."

The roentgenologic examination by Dr. Willis F. Manges showed megacolon.

Dr. Manges reports: "November 6, 1923: There is undoubtedly a megacolon present. This was not only apparent from the large amount of gas present before the injection but was also verified by the injection of barium. I injected only as far as the splenic flexure and I stopped at this point for the reason that it seemed to me that the child was beginning to have some little



FIG. 1.—Case G. L. C. Exposure made in November, 1923, showing the colon under natural conditions before barium enema had been administered. Note the distention of the bowel with flatus, the absence of the haustral markings and the refolding of the gut.



FIG. 2.—Case G. L. C. Roentgenogram made in November, 1923, after barium enema. Only the rectum, sigmoid and ascending portions of the colon have been distended by the barium, which did not go beyond the splenic flexure. Note the refolding, the absence of haustral markings, and the enormous capacity of the gut.



FIG. 3.—Case G. L. C. Exposure made in February, 1924. Filling of the entire colon as far as the cecum. Note reduction in capacity of the gut, but still the refolding and absence of haustra.



FIG. 4.—Case F. C. L. From another patient aged twelve years, with dilatation of the ascending, and the right half of the transverse portions, of the colon. The descending portions, as well as the sigmoid and rectum, are normal as to size and tone. Comparison should be made between the size of this sigmoid in a child of twelve years and that in the other roentgenogram of the case aged three years reviewed in this article.

embarrassment in breathing. I think it is important, however, to note that the colon was entirely empty of fecal matter when he came to me for study."

Immediately following the Roentgen-ray examination there was great pain and distress, and embarrassed respiration because of the enormous distention of the abdomen. He was unable to empty the bowel voluntarily, even though the intraäbdominal pressure was very great. A rectal tube was inserted and large volumes of gas with over 1500 cc. of liquid feces and barium solution were drained off, the latter part of it aided by pressure of the hand on the now flaccid abdomen. The hypertonic anal sphincter seemed to be the cause of the obstruction, for as soon as the tip of the tube entered the rectum the contents gushed through.

Subsequent Course and Treatment. He was placed on sodium sulphate, ½ dram night and morning; increasing doses of tincture of nux vomica; acidophilus milk; meat-free and fairly high-starch diet; sine-wave electricity to the abdomen and general massage. To move the bowels the plan suggested by Dr. Horace Soper, of St. Louis, was followed. This was the injection of 2 ounces of the following solution: Saturated magnesium sulphate solution, 1 part; saturated sodium sulphate solution, 1 part; warm water, 2 parts. This plan of treatment insured a copious bowel evacuation each day. At the end of a week the patient had gained sufficient strength to permit the administration of nitrous oxid and oxygen anesthesia, while a search was made for a possible anal fissure. None was found. Divulsion of the anal muscle was then attempted, but not accomplished because under the anesthetic the muscle could be stretched to its utmost limit but would not tear. Again it was noted that once the spasm of the sphincter was removed the contents of the rectum and sigmoid were discharged with explosive violence. Within another week the child had his first voluntary bowel movement, and was playing about without exhaustion, going up and down stairs freely. The abdomen was much less distended at all times, and the rectus muscles could now be felt as very thin bands; all his muscles were of fairly good tone.

Cod-liver oil was added to his diet, and a very small amount of meat was allowed twice a week. The sodium sulphate by mouth was stopped and fruit paste substituted for it. By January, 1924, his weight was 35¾ pounds, and this represented a gain of nearly 4 pounds in two months. At times there were small formed, voluntary, finger-sized bowel movements.

In February, 1924, another Roentgen-ray examination was made in an endeavor to check up on the condition of the colon.

Dr. Manges reports as follows: "February 2, 1924: The sigmoid and descending colon, so far as I can tell, permit of the same distention that they did at the former injection. There was,

however, considerably less gas in the colon and I succeeded in getting the barium mixture into the entire colon. The point of greatest dilatation is the lower end of the sigmoid and rectum; then gradually diminishes so that at the cecum the dilatation is not so great—I should say less than half of what it is at the sigmoid."

While there had been a great change in the child for the better—he was robust and played outside for the greater part of the day in the cold, he ate and slept well, and occasionally had an unassisted bowel movement—it was felt that the sphincter was still disproportionately overactive as compared to the activity of the sigmoid. In an endeavor to correct this defect, I asked Dr. Allen to incise the sphincter.

Dr. Allen's report of operation: "March 22, 1924: The muscle was divided on the left side midway between the anterior and posterior boundaries, taking care to make incision at right angles to the fibers of the muscle. The wound was kept open and allowed to heal by granulation; recovery was uninterrupted and function good."

There was, undoubtedly, improvement in the bowel function following the sphincterotomy. Treatment with sine-wave electricity was persisted in, and the abdominal muscles became progressively firmer and stronger. All medicines were withdrawn with the exception of fruit paste, which was required to afford a voluntary bowel movement. But by June, 1924, the anus was as tonically contracted as ever.

Since then there have been transient attacks of constipation, but these have always been easily overcome by enemata. Fruit paste is given almost nightly to insure an evacuation, even under the most favorable conditions. The child now weighs 40 pounds, is sturdy and physically the most active of all the children of this family; while he is still constipated, the original condition has been greatly improved, but is decidedly not cured.

Theoretical Discussion. Some form of operative procedure will probably be necessary to bring about a complete cure in many cases of megacolon. There are many types of operation to choose from—colostomy, colon plication, colopexy and enteroanastomosis with or without resection. Finney[1] favors the two-stage operation of ileosigmoidostomy: (1) The anastomosis, and (2) the resection of the colon.

I should like here to offer a suggestion (first brought to my attention by Dr. George Dorrance) as to a form of surgical treatment of megacolon which may be rational—the operation of ramisection or sympathetic ramisectomy, as introduced by Dr. N. D. Royle.[23] Devine[31] has given it some consideration, and by destroying a part of the sympathetic supply of the slow stomach has lessened its emptying time.

The work of Royle and of the late Dr. John I. Hunter[24] has

shown that spasticity in the muscles of a limb, paralyzed through a central or cortical lesion, may be overcome by removing the influence of the sympathetic nerve supply to the limb. This is done by severing the sympathetic fibers, the gray ramus of the several intervertebral or spinal nerves, going to make up either the brachial or the sacral plexus. After thoroughly reviewing the work of these two men, and studying some of the theories of the function of the sympathetic nerve supply of the bowel as propounded by Gaskell,[25] Bayliss,[26] Macleod,[27] Langley[28] and others, the conclusion is forced upon me that in megacolon we have a condition that very closely resembles in its functional aspect spasticity in centrally paralyzed limb muscles. If this be so a similar method of treatment would seem rational. In one of Royle's operations he cut the white ramus (the second lumbar of the right side) and this procedure promptly gave relief from a very obstinate constipation of long standing, without affecting the bladder function.

The sympathetic fibers supplying the bowel are purely motor in function. They originate in the lateral horn of the gray matter of the spinal cord and leave the anterior portion of cord as the white ramus, in company with the voluntary spinal motor fibers, and pass through the intervertebral foramina on either side of the spinal column. On the anterior surface of the body of the vertebræ they form the sympathetic cord, and from this cord there passes back to the intervertebral or spinal nerve, the gray or nonmedullated ramus. This ramus contains the sympathetic nerves to the skin (pilomotor and sweat), the vasomotor (constrictor) and muscular fibers. These sympathetic nonmedullated fibers accompany the spinal nerve to all of its various musculocutaneous distributions. In the muscle its terminations are separate from the end-plate terminations of the motor nerve, and its function is that of maintaining the plastic tone of the muscular fibers, that is, once the muscle becomes flexed through voluntary action, it tends to stay flexed through action of the sympathetic impulses; or, again, once the muscle is extended through voluntary nerve impulse, it tends to stay extended through the constant activity of sympathetic impulses. The muscle tends to maintain this or that position—it tends to stay put—through this sympathetic influence. One can conceive of a lead-pipe spasticity resulting from sympathetic hyperactivity, or even of a cataleptoid state, as spoken of by Sherrington.[29]

It is thought that the function of the sympathetic as far as the bowel, too, is concerned is practically identical with that of the muscles of the extremities; thus, if the bowel becomes distended through feces being pushed down into a certain segment, as the result of intermittent impulses of the parasympathetic nerves (bulbosacral or vagopelvic, enteral or autonomic) then the con-

stantly acting sympathetic impulse tends to maintain this posture of the bowel segment, it tends to maintain the muscular tube in a certain degree of contraction or dilatation until another intermittent motor impulse comes along through the parasympathetics to cause the tube to further contract. In the sigmoid this impulse would come through the pelvic nerves—nervi erigentes—derived from the first, second and third sacral spinal nerves (running directly to Auerbach's plexus in the bowel wall), having the same propulsive function for the colon, or at least for its lower portion, that the vagus (tenth or pneumogastric) nerve has for the upper part of the gut tract. Stimulation of the pelvic nerve produces contraction of the lower colon (sigmoid and rectum) and coincident relaxation of the anal musculature. The sympathetic nerve supply of the sigmoid comes from the abdominal sympathetic chain, through the inferior mesenteric plexus, the hypogastric nerves and the hypogastric and pelvic plexuses. In function, the sympathetics inhibit the action of the pelvic nerve impulses, maintain the sphincter in a state of tonic contraction and keep the bowel musculature in a certain "posture" as regards distention without in any way increasing pressure within the bowel. This was well shown by Masso and Pellacani[30] in the case of the urinary bladder of the dog, which has a similar innervation—that whether it contained 10 cc. or 90 cc. of water the intravesical pressure remained constant, namely, that of 10 cc. when 80 cc. more were added. This was not so, however, for dead bladders. Thus the sympathetic innervation provides for the muscle assuming this or that "posture," and the term plastic tonus has been given by Sherrington to this postural reflex contraction.

So, one can conceive of a sigmoid, or of a colon, having disproportionately functioning parasympathetics and sympathetics, having markedly unbalanced impulses given to it and to its anal gate tending through overaction of the sympathetic supply to become unresponsive, then to dilate and hypertrophy. This condition is found in megacolon. The same overactivity of the sympathetics would cause hypertonicity of the anal sphincter and thus inhibit the power of the pelvic nerve to relax that muscle. This condition was found the cause of the megacolon here reported.

Hunter[24] has shown, as have others, that removal of the influence of the sympathetic nervous system allows for very much more active function of the bowel by withdrawing the inhibition which the sympathetic places on the activity of the parasympathetics. He believes that by ramisection of the first or second lumbar white ramus this can be accomplished.

I shall welcome the views of others on this point, and am hoping for criticism and discussion to be born by this statement.

It is a difficult operation to perform, but in the hands of a careful man it is a possible operation, as Royle has shown, and extremely

safe from a mortality viewpoint as compared with the various bowel anastomoses. This operation appears to me as ideally suited to cases of megacolon, or, indeed, even to the obstinate cases of atonic constipation, and, when the time comes, unless it can be shown that the premises are faulty, and that the conclusions are illogical, I believe that I shall advise that ramisection be done.

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THE TREATMENT OF ABSCESS OF THE LUNG.*

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In a previous communication[1] (two years ago) we reported our experience with pulmonary abscess based upon a series of 60 cases.

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Since that time we have treated 40 additional cases of this disease which has offered the opportunity to extend and to some extent modify the rationale of treatment which we outlined at that time.

The number of cases which have come under our care has impressed us as indicating that this disease is a more common one than is generally recognized and has increased our interest in the problems surrounding its causation, in the hope of contributing to our knowledge of possible methods of prevention. These studies we expect to make the subject of a future communication.

We have also been increasingly impressed with the seriousness of this condition. This is well brought out by a review of the literature dealing with the treatment of pulmonary abscess by various methods of treatment which indicates a mortality varying from 15 to 60 per cent in reported series of material size.[2] The fact that in this new series of 40 cases we are able to report a mortality of only 10 per cent influences us to offer a description of the system of management yielding these results, which are more favorable than any that we have heretofore obtained and also better than any that we have been able to find reported by others.

System of Management. The term "system of management," rather than that of "method of treatment," is used advisedly for the reason that we are impressed by the variability of response of these cases to any given therapeutic method and by the frequent necessity of modifying or combining various methods in order to obtain the best results in any given case. We have found it futile to accept any one method as generally applicable, but in the study of our cases have been able to employ all of the generally recognized methods to more or less advantage. We have, therefore, no new method to suggest, but rather a method of approach which has left us free to apply any or all known methods according to the indications presented.

We believe that this would have been difficult, if not impossible, had we not undertaken this study as a joint problem for internist and surgeon, for this disease lies in that borderline zone of medicine and surgery which presents problems of constant and continuous interest to each. All of our cases have, therefore, received equal and regular supervision from us both and no plan of treatment has been undertaken in any case excepting as agreed upon in joint conference.

We have also found it increasingly important to introduce a third viewpoint into our case studies in that of the bronchoscopist and we have been exceedingly fortunate in having the close coöperation of Dr. John Kernan in this series of cases, who has seen many of them with us and has bronchoscoped several when the indications seemed to demand this procedure.

The system which we have come to adopt is first and foremost absolute bedrest, combined with postural drainage. As soon as the

diagnosis is established, all cases are placed under this regimen and watched very carefully, with special reference to the behavior of the temperature, the amount and character of the expectoration and the changes exhibited in the Roentgen-ray films, which are taken at least once a week. Physical examinations of the chest are, of course, made frequently but yield less valuable information than these other observations.

The progress of each case is studied in joint conference once a week, or oftener if special developments occur, and if the progress is not deemed satisfactory, additional methods of treatment are considered. They are bronchoscopy, operation by incision and drainage or artificial pneumothorax. It is unusual that any of these methods are employed before the expiration of three or four weeks of the more simple medical treatment by rest and posture.

We also consider it important to make Wassermann blood tests in all cases and to employ systematic antisyphilitic treatment in every one which reacts positively. This treatment appears materially to enhance their prospects of cure without radical procedures.

With this general plan in mind it will assist to a better understanding of our specific methods to consider the elements in our system of management separately and to evaluate the importance of each and its relation to the plan as a whole.

Rest. It is only in the past two years that we have come to what we now consider a proper appreciation of the value of prolonged bedrest in the treatment of lung abscess. We were influenced considerably by Pritchard's[3] valuable contribution to this subject and have come to agree very heartily with his conclusions.

During the febrile period bed treatment is obviously indicated and probably universally employed, but in the majority of these cases the fever subsides more or less promptly even with inadequate drainage of pus through a bronchus, and it is quite common to note a consistently normal temperature without a correspondingly satisfactory decrease of cough and expectoration, or of improvement in the character and extent of the lesion as shown by the Roentgen-ray films. Under such circumstances, the general condition of the patient is naturally better and often confinement to bed becomes irksome, but we believe that persistence in bed until the cough, expectoration and Roentgen-ray findings, as well as temperature, all indicate the clearing up of the necrotic process in the lung is most important and will very materially assist the postural treatment in obtaining a socalled medical cure. Moreover, we believe that rest plays a valuable role for many weeks after all symptoms have been absent, especially if the Roentgen-ray densities have not absolutely and entirely cleared. In such cases relapse into acute symptoms may occur even many weeks after all cough and expectoration and fever have disappeared and we have for this reason had several occasions to regret a premature discharge from hospital supervision or return

to the normal activities of life. We therefore advise a prolonged period of weeks or even months of an after cure very similar to that employed in the management of a partially arrested case of tuberculosis, until the last vestige of pathological Roentgen ray shadow has disappeared or what remains may be fairly certainly interpreted as representing a permanent fibroid change.

In this after-cure hard physical work or violent exercise are excluded and rest in the recumbent position is required for considerable periods each day. These are gradually diminished and increasing exercise allowed until a normal degree of active life is attained and a permanent cure is effected.

Postural Drainage. Cough with the expectoration of pus occurs in all cases of lung abscess in which there is a communication with a bronchus. Complete drainage of the abscess may result in this manner and a spontaneous cure thus effected in a limited number of cases. As a rule, the cough, while producing the expectoration of foul pus in large quantities, only succeeds in eliminating the amount which constantly wells up into the bronchi, leaving the abscess cavity itself still completely or partially filled with pus, with consequent increasing necrosis and collateral inflammatory reaction in the lung itself. Certain positions of the body will very frequently aid in the more complete emptying of the cavity by the cough and thus the proportion of cases cured by this natural method of drainage may be materially increased. Patients will themselves frequently note that certain positions increase the amount and ease of expectoration and these observations are often valuable guides to postural treatment.

In general, we invert the patient completely with the head hanging straight down to the floor bending at the waist over the edge of a bed. A twist of the body so as to bring the affected side to a higher level than the opposite one is often desirable. Sometimes lying on the back with the head down, with the body held in position by the bend of the knees is more effective. This can be accomplished by the reverse use of the break of a Gatch bed, or by lying over a stiff chair inverted and placed upon a flat bed. Sometimes the best results are obtained by positions which have no logical explanation as far as the location of the abscess is concerned, and we have been interested to note that upper lobe abscesses are quite as apt to drain by the inverted posture as are those situated in the lower lobes. In any event, considerable time must be spent in patient experimentation with each case to discover the best position for that particular patient.

After this has been determined, this posture is prescribed at regular intervals, usually every three or four hours at first, and is maintained for periods varying from five to fifteen or twenty minutes. The discomfort felt in the head from the inverted position quickly disappears and patients rarely complain of it after the

first day or two. An observant patient soon learns from his own sensations when he needs drainage and the interval and duration of each treatment is modified accordingly.

The effect of this treatment is very striking when successful. The more complete emptying of the cavity gives a complete cessation of cough for hours at a time, allowing a very gratifying relief from the constant and harassing paroxysms which so often mark this disease. The amount of expectoration which is carefully measured and noted for each twenty-four hours, at first very materially increases and then in a few days gradually diminishes until it may entirely disappear in a week or ten days. The fever subsides and the patient is transformed from a miserable and acutely ill person to a comfortable convalescent. Many times these desirable results are only partially obtained and in still other cases no appreciable result in amelioration of symptoms is noticeable. In such cases after adequate trial it is necessary to supplement this treatment by one or the other of the other methods to be later considered.

We are accustomed to persist in this treatment for at least three or four weeks before discarding it, because not infrequently good drainage may be established quite suddenly in cases which have shown no results during the first weeks. In the evaluation of this, as well as all other methods of treatment, the comparative Roentgen ray films are the best single guide.

As already described, absolute bedrest is prescribed in the intervals between the postural treatments.

This combination of rest and postural drainage constitutes our basic method of treatment to be first used in practically all cases and the result obtained affords the point of approach to our consideration of additional methods. In the series of 40 cases here reported it was the only treatment employed in 14 cases, of which 8 were cured and 6 markedly improved.

Bronchoscopic Treatment. Our earlier experience led us to doubt the general applicability of the bronchoscope in the treatment of lung abscess. We were also impressed by the fact that some fatalities occurred and that very frequently it was a most distressing ordeal for the patient.

We have considerably modified our previous point of view in the experience which we have had through the close coöperation of Dr. Kernan in the study of many of our cases. While we cannot share the enthusiasm of some who consider the use of the bronchoscope as the most important method to be first considered in these cases, we do feel that in many it may facilitate drainage when it is not promptly established by the rest and postural plan.

We believe, however, that the possible dangers and discomforts of this method are eliminated only if it is in the hands of a very skillful operator of large experience and mature judgment. We

feel that the occasional bronchoscopist should not attempt the treatment of lung abscess.

That this method in skilled hands is useful and not dangerous in properly selected cases is evidenced by the considerable experience now reported by such bronchoscopists as Chevalier Jackson,[4] Lynah,[6] Carmody,[7] Yankauer,[8] Kernan and others, by the testimony of such thoracic surgeons as Lilienthal and Willy Meyer[9] and by the experience of internists such as McCrae[5] and Funk.[10] They emphasize the importance of early treatment in acute cases and report occasional very prompt cures, often great improvement and in chronic cases amelioration of symptoms with occasional cure.

This has also been our experience but we emphasize the importance of rest and posture as basically important and the use of the bronchoscope, which can only be employed at about weekly intervals, as a most valuable adjunct to this treatment in many cases by helping to establish more prompt and direct drainage.

It is our experience that it is the passage of the tube, combined with suction, which is valuable, and that lavage and the introduction of such medicaments as antiseptics, local stimulants, bismuth and the like, have no value and may do harm. We do not favor bronchoscopy in abscesses situated near the periphery of the ung, it is contraindicated in those not communicating with a bronchus, and is less apt to be successful in lesions situated fairly high up in the upper lobes. It is most useful in abscesses situated near the main bronchi, especially those in the lower lobe, but it is to be noted that it is just in this class of cases that rest and posture is most apt to succeed.

For the diagnosis and cure of abscess due to foreign body inhalation, bronchoscopy is the method of treatment, and for the diagnosis of new growth in the lung simulating a true abscess it is invaluable. It is also of value in accurately localizing the lesion in cases which come to radical surgical operation. We advise this method, therefore, in acute abscesses which do not promptly drain with posture, when the location is not near the periphery, in chronic cases for the amelioration of distressing cough and expectoration and for the diagnosis and localization of the lesion.

Under this plan, 7 of the 40 cases reported in this series have been bronchoscoped. One of these cases was cured, 2 were markedly improved, and 4 were not improved and later came to radical operation.

Artificial Pneumothorax. The success of collapse therapy in certain cases of pulmonary tuberculosis very naturally has led to its consideration as a possible useful procedure in other pulmonary conditions and among them lung abscess.

We have employed this method in some cases, but tentatively, in order to have actual experience as a basis of judgment, rather than with great confidence in it as a rational procedure. The reason

for this somewhat experimental method of approach is found in our conception of the radically different objects to be attained in pulmonary tuberculosis as opposed to abscess of the lung. In tuberculosis, rest and immobilization of the lung appears to us to be the prime consideration and for this often partial pneumothorax without any actual compression of the lung is adequate.

In abscess, drainage is the desired object, and by artificial pneumothorax this can only be facilitated by pressure properly applied upon the right point and in the right direction. We do not feel that this can be accurately gauged in artificial pneumothorax. Moreover, it sometimes happens that the air introduced works around into the pleural space near the mediastinum and may actually cut off drainage already partially established, resulting in an exacerbation rather than a relief of symptoms. This has been our experience in some cases and has been reported also by others. We also feel that the expulsive action of the cough, which is, after all, the one most important factor in lung drainage, may be hampered in a lung partially immobilized by a pneumothorax.

Our most serious objection, however, is the very real danger that the pleura may be ruptured when this method is employed in abscesses, with a resulting acute septic empyema necessitating immediate operation and under circumstances which render the danger to life exceedingly great. We have had a few such experiences and reports of similar cases occur rather frequently in the literature.

Tewkesbury[11] is perhaps the warmest advocate of artificial pneumothorax in the treatment of lung abscess and he reports very considerable success. He advocates its use, as soon as the diagnosis is established, the earlier the better, if possible before any pleural adhesions are formed. He does not, however, state that it is not to be used in more chronic cases. Others have also reported successful results but usually in very small series of cases and among these are also some of the unfortunate ruptured cases above noted, and we cannot escape the impression that many cases have been treated without careful study of the other possible methods of treatment and without due regard to the dangers that may be involved.

Upon the whole, therefore, we believe that this procedure carries with it too great a risk to warrant its employment as a routine procedure in the treatment of lung abscess, at the same time realizing that with a fortunate combination of circumstances, especially in lesions situated near the hilum, brilliant results, as in one of our own cases, may be obtained by its use.

In this series, we employed artificial pneumothorax in combination with rest and posture in 10 cases. Of these 1 very promptly recovered and 2 were improved. The remaining 7 were not improved, of these 2 were also bronchoscoped without result and all were later operated on.

Surgical Operation. The treatment of lung abscess has often been considered mainly a surgical responsibility. We have outlined above our plan of management which has for its main object the cure of the condition without recourse to this radical procedure, which is attended by considerable risk and which, even when successful, always results in long weeks or months of purulent discharge with frequent dressings and considerable discomfort, and which sometimes ends in a bronchial fistula, difficult or even impossible to heal. It is obvious that a cure obtained without operation is a much more simple and satisfactory procedure and that this is possible to obtain in a considerable percentage of cases has been demonstrated. Nevertheless, it is our experience that with all our increased effort to obtain a cure without operation, it still eventually becomes a necessary resort in from 40 to 50 per cent of our cases.

The surgical treatment consists in incision and drainage, with the resection of two or more ribs, in one stage if the pleural cavity is walled off by adhesions, otherwise, in two stages. Local anesthesia is safer than general anesthesia even with nitrous-oxide gas and oxygen. A soft rubber dam is the best form of drain, and we have abandoned the use of gauze, employing it only to control hemorrhage.

We found this operation extremely dangerous and usually unsuccessful in the acuter phases of the disease; that is, during that period when there was present about the softened central suppurating focus a more or less extensive zone of edematous, soggy, infected lung in which the smaller bronchi were filled with pus and the alveoli were distended with seropurulent exudate, while the walls of the alveoli were swollen and edematous. None of these cases was seen prior to rupture and establishment of communication with a bronchus.

Our experience has led us to believe that incision of the abscess at this time fails to drain effectively the entire infected area, and that, with a free opening established, the effectiveness of coughing in emptying these areas is greatly reduced. In many of our cases in which the abscesses were opened during this stage, there was a pronounced improvement for a few days, the expectoration was diminished; the temperature became normal, and the patient apparently was making a satisfactory recovery. But this period was followed by a wide extension of the pneumonic process, sometimes ushered in by a chill and a fatal termination in from three to five days or a week. At necropsy, there was found a widespread massive involvement of the entire lung or both lungs, in which the bronchi were filled with pus and the alveoli either showed the changes of an acute pneumonia or were swollen, edematous and infiltrated with leukocytes. In some cases, there were multiple small abscesses widely disseminated throughout the lungs.

After postural drainage, even if it does not effect a cure in itself, there is usually a definite improvement in the constitutional symptoms and a clearing of this secondary zone of infiltration about the abscess, which renders an operation much more liable to succeed.

There is a period in lung suppuration when the alveoli in the immediate vicinity of the abscess are collapsed but the respiratory epithelium is still intact, and they are therefore capable of reaëration and this is the most favorable time to operate. If the suppuration continues, this epithelium disappears and the alveoli are obliterated; and there is found a true connective-tissue layer composed of the fused alveolar walls, observed in chronic abscesses; a condition most unfavorable for a complete cure and one which favors the establishment of a permanent bronchial fistula.

The problem is to give each patient an opportunity to reach this more favorable stage and at the same time not allow the disease either to go on indefinitely or to drift into the chronic abscess with thick fibrous walls, which is unfavorable for radical cure by operation or any other method of treatment. The decision as to when this optimum time for operation has arrived is in our opinion the most difficult and important factor in successful treatment. Our increasing success in three successive series of cases studied carefully during the development of our present methods is mainly due to better judgment in making decisions upon this vital point. We find the comparative Roentgen-ray pictures the best guide. Acute cases show diffuse densities shading off gradually into the surrounding normal lung without any sharp line of demarcation. This we believe represents the zone of pneumonic infiltration above described.

Under rest, posture and bronchoscopy it is almost always possible to obtain a change in the Roentgen-ray picture represented by a diminution in the area of the collateral zone of inflammation and a sharper line of demarcation between it and the surrounding normal lung. When this change is obtained and further clearing tending toward cure does not occur after three or four weeks of observation, we believe that the time has arrived for operation. The most important point is not to operate during the acute inflammatory stage. Upon the other hand, if operation is too long delayed the chronic stage is reached with the increased difficulty of ultimate cure by operation.

Proceeding under this plan, 20 cases of this series, or 50 per cent, came to operation. Of these, 9 were cured, 7 markedly improved, and 4 died. A bronchial fistula resulted in 3 of the improved cases. In the 20 operative cases the preceding treatment had been rest and posture in 11 cases, rest and posture combined with bronchoscopy in 2 cases, artificial pneumothorax had been unsuccessfully employed in 5 cases, and in the remaining 2 cases rest, posture, bronchoscopy and artificial pneumothorax had all been tried without success.

Causes of Operative Deaths. Four of the 20 patients operated upon died, an operative mortality of 20 per cent. These 4 operative deaths comprise all the deaths experienced in our entire series. By our plan of management it is evident that the mortality would be mainly, if not exclusively, included in the operative group, for the reason that cases which do not respond to the other methods of treatment are the ones considered suitable for operation. This brings all of the more serious and difficult cases into the series operated upon, which naturally increases the hazards of that group.

We feel that although our operative mortality has been materially diminished as compared with our previous experiences, nevertheless there is still definite room for further improvement and our especial study at present is directed toward that end.

An analysis of the causes of death in the 4 fatal cases is consequently considered of importance.

Our first operative death was in a case in which no pleural adhesions were found, although expected. Too wide an exposure was made, pneumothorax resulted, the abscess was not reached and death occurred in three weeks. We consider this death due to faulty technique.

The second death was due to a general streptococcus septicemia following operation. This is an unusual complication which, however, will undoubtedly occasionally occur, and we do not see how it could be guarded against.

The third case illustrates the dangers of artificial pneumothorax in these cases. After five such treatments the patient suddenly developed an acute pyopneumothorax due to rupture of pleuritic adhesions. This necessitated an immediate emergency operation which discovered a very foul infection of the pleural cavity with anaërobic organisms and the patient died, as they are very apt to do in such cases. The responsibility of this death should be laid against pneumothorax treatment rather than the resulting surgical operation.

The fourth and last case was a heart-breaking one to lose. A case with very large abscess had been carefully treated by rest and posture and had reached a stationary stage with marked general improvement but no change in the Roentgen-ray picture after several weeks. The collateral zone of inflammation had subsided and the line of demarcation from the surrounding lung had become sharp. We considered it an ideal case for successful operation. The patient did splendidly and was apparently upon a sure road to recovery when twenty days after the operation he suddenly died from a cerebral embolism. This accident is one of the real but fortunately comparatively rare hazards of operation in lung abscess. We do not know how it can be prevented.

In summarizing our experiences with these 4 fatal cases we conclude that in 2, death might have been avoided but not in the

other 2. We believe that an operative mortality of 10 per cent is probably the best that can reasonably be expected in any large series of lung abscesses and that it should be our aim to attain this result.

TABLE I.—RESULTS OF OPERATION.

Series.	Number of cases.	Number operated upon.	Per cent cases operated upon.	Cured.	Improved.	Died.	Operative mortality, per cent.
First . .	29	14	48.3	4	0	10	71.5
Second . .	31	13	41.9	7	1	5	38.5
Third . .	40	20	50.0	9	7	4	20.0
Total .	100	47	47.0	20	8	19	40.0

In the accompanying Table I, the results of operation which we have obtained in three series, two of which have already been reported, are presented. The progressive improvement in the three series is striking and we ascribe it mainly to a wiser selection of the time and stage of the disease suitable for operation.

General Analysis of Clinical Material. Certain general considerations are here presented in order to record the type of clinical material with which we have been dealing in this series of cases.

Etiology. Fourteen cases gave no history of any previous condition which could be considered as a factor in the causation of the pulmonary abscess. These cases we have classified as idiopathic abscesses and the percentage of them corresponds very closely to the number noted in our previous series.

Thirteen cases definitely followed an acute pneumonia.

Five cases were due to a tonsillectomy and 5 were secondary to some other surgical operation.

One followed tooth extraction, 1 seemed directly attributable to prolonged submersion in contaminated water, and 1 followed severe trauma to the chest.

No cases in this series were due to the inhalation of a foreign body.

Duration before Treatment. It is generally recognized that any method of treatment is more successful the earlier it is instituted. Chronic cases are difficult to cure. The length of time that the abscesses have existed therefore would have a definite influence upon the results to be expected.

Of these 40 cases the abscess had existed less than one month in 15 cases, from one to three months in 10, from three to six months in 6 and more than six months in the remaining 9 cases. These last may be considered as chronic cases which thus constituted $22\frac{1}{2}$ per cent of the series.

Location of the Lesion. In 29 cases the lesion was situated in the right lung. Of these, 15 were in the upper lobe, 11 in the lower lobe and 3 in the middle lobe.

In 11 cases the left lung was involved, in the upper lobe in 4 cases and in the lower in 7.

Sex. In our experience, lung abscess is much more common in men than in women. In this series, 31 cases were in men and only 9 in women. This is in accord with our previous experience and with that of other observers.

TABLE II.—SUMMARIZED RESULTS OF TREATMENT.

Series.	Number of cases.	Cured.	Improved.	Not improved.	Died.	Per cent mortality.	Per cent cured or improved.
First . .	29	11	2	4	12	41.4	45.0
Second .	31	14	5	4	8	26.0	61.0
Third .	40	19	17	0	4	10 0	90.0
Total .	100	44	24	8	24	24.0	68.0

Summarized Results of Treatment. The results which we have obtained by the various methods employed have already been indicated. In Table II, the general results obtained are tabulated in comparison with those previously reported in our other two series.

The progressive improvement already noted in the summary of our operated cases is reflected in this table also. This is particularly noticeable in the diminution of the mortality which is only 10 per cent in this last series. In considering the number of cured and improved cases it is to be noted that the percentage of absolute cures reported is only slightly larger in our last series, but many of the cases classified as improved are still under treatment and will, we believe, eventually become cured. This applies especially to the operative group, 7 of which, though doing well, still have discharging wounds and in consequence cannot be included among the cured cases.

Summary and Conclusions. 1. The successful treatment of cases of abscess of the lung is materially aided by their joint management by internist and surgeon, with the close coöperation of a skilled bronchoscopist.

2. A systematic plan of prolonged rest, combined with postural drainage, is the basic method of treatment. Into this plan the other methods may be advantageously introduced in properly selected cases.

3. Bronchoscopy is of real value as an aid to drainage in certain cases. Artificial pneumothorax has a very limited field of usefulness.

4. Approximately from 40 to 50 per cent of all cases will eventually need radical surgical treatment. Correct judgment of the indications for operation is the crucial element in successful treatment. In general, it is based upon the avoidance of surgical intervention during the acute phases of the disease but without delaying too long and thus allowing the case to drift into the chronic stage.

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BACTERIAL VACCINES IN ASTHMA.[1]

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There is so much controversy regarding the use of bacterial vaccines in asthma and I have had so many inquiries from physicians on the subject that I decided to prepare this paper telling in detail a method of diagnosing and treating bacterial asthma that has proven very satisfactory in my hands.

Diagnosis. I will only refer to such points as have a bearing on the diagnosis of bacterial asthma.

History. An exhaustive history should be taken on every asthma case, as invaluable information can frequently be obtained in this way. The age of onset is important, as asthma that starts after the age of forty years is almost always nonsensitive or bacterial in type. This is just what we would expect, as it does not seem probable that a person after forty years would become sensitive to some food or air-borne substance to which he had been exposed all his life. On the other hand, bacterial infection of the respiratory tract would be more likely to occur in the later years of life due to the lowered resistance at this time. Walker stated that none of his patients who developed asthma after the age of forty years were protein-sensitive. There are exceptions to this rule, however, as I have seen a few patients who developed asthma after the age of forty that was definitely proven to be due to sensitization to food or air-borne substances.

Bacterial asthma may be perennial or seasonal in type. The seasonal type of bacterial asthma is frequently limited to the winter months, also commonly occurs during the changeable weather of early spring and late fall. One differential point between the spring and fall seasonal bacterial cases and pollen asthma is that the bacterial cases are more irregular in their time of starting and stopping than the pollen sensitive cases. When itching of the eyes is met with, the case is not likely to be a bacterial one, as definite itching of the eyes is very suggestive of sensitization, in fact is almost always present where sensitization exists to some air-borne substance. The nasal secretion in bacterial cases is likely to be thick, sticky, and frequently yellowish, in contrast to the thin, clear, watery secretion of the sensitive cases, although there may be a thin, watery secretion with a streptococcus infection. Likewise, the sputum in the bacterial case is more likely to be of a greenish-yellow, purulent nature than the grayish-white, jellylike sputum of the sensitive asthmatic. The bacterial asthmatic usually

[1] Read before the American Association for the Study of Allergy, Atlantic City, N. J., Tuesday, May 26, 1925.

has a great deal more cough and expectoration than the sensitive individual. In the bacterial type, as a general rule, cough initiates the attack, whereas in the sensitive type, shortness of breath and wheezing are the first symptoms noted and cough does not usually occur until the attack is breaking up. Between attacks, the bacterial asthmatic frequently has more or less cough and expectoration, whereas the sensitive asthmatic is usually free of these symptoms. In bacterial asthma the most common time for the attacks to begin is in the early morning hours, whereas in sensitive asthma the attacks come on at any time, out of a clear sky, dependent, of course, upon ingestion of, or exposure to, some offending substance. Sensitive asthmatic attacks are usually more abrupt in their onset than the bacterial type. Bacterial cases are usually more susceptible to sudden changes in the weather than sensitive asthmatics. Bacterial asthmatics are also more subject to "colds," sinus trouble, and the like, than the sensitive patients. Bacterial cases will commonly give the history that they never have asthma except when they take "cold." The sensitive asthmatic also occasionally gives this history, when in reality the attacks are not due to taking "cold" at all, as the symptoms simulating a "cold" such as sneezing, running of the nose, watering of the eyes, are merely reactions of the mucous membranes to some offending substance. These sensitive cases may usually be differentiated from the bacterial ones, however, by the fact that in the former the apparent "cold" and asthma may all develop within a few hours, whereas in the latter it usually requires several days for a head "cold" to get down in the bronchial tubes and produce asthma.

Physical Examination. An examination of the nose and throat and the heart and lungs should be included in the study of every asthmatic, especially where the cause is unknown, and all suspicious cases should be referred to specialists for this purpose. A red, inflamed, congested nasal mucous membrane, nasal polypi, inflammation about the orifices of the nasal sinuses, pus exuding from these orifices or lying free in the nasal cavity, pharyngeal inflammation, injection of the tonsillar pillars or definitely diseased tonsils, all point toward bacteria as the cause of the asthma, although of course bacterial infection may be superimposed on a true sensitive asthma. In the true sensitive asthmatic when there are nasal symptoms such as sneezing and rhinorrhea, the nasal mucous membrane appears bluish-gray, boggy or even water-logged, quite a different picture from the membrane of bacterial infection.

Skin Tests. What tests to make and what tests not to make is an important question to be decided in each individual case. I am absolutely opposed to the principle of testing everybody with everything. Every substance should be tested to which the slightest suspicion can be obtained in the course of an exhaustive history. In those patients whose asthma began before the age of

forty years, skin tests should also be made with all food proteins, animal epidermals, pollens, orris root, house dust and miscellaneous substances that the individual patient eats or comes in contact with at least once a week during the season of the year in which he has asthma, or throughout the year if the disease is of the perennial type. If positive reactions are not obtained that are sufficient to account for all of the patient's asthma, tests should also be made with stock bacterial proteins. In those patients whose asthma began after the age of forty, other than making those tests indicated by the history, and tests with stock bacterial proteins, it is sufficient to test the foods and other substances which the patient eats or to which he is exposed every day during the period of the year in which he has asthma.

In testing with stock bacterial proteins I routinely use the following: Staphylococcus pyogenes aureus, Staphylococcus pyogenes albus, Staphylococcus pyogenes citreus, Micrococcus catarrhalis, Micrococcus tetragenus, Streptococcus hemolyticus, Streptococcus nonhemolyticus, Streptococcus viridans, Pneumococcus Type I, Pneumococcus Type II, Pneumococcus Type III, Friedländer bacillus, Diphtheroid bacillus, Bacillus coli communis.

I also make a von Pirquet test at the same time. That portion of the arm where the tuberculin and the glycerine-bouillon control are to be applied is first wiped off with ether. When a definitely positive reaction is obtained to a von Pirquet test, especially if it occurs immediately, the sputum should be carefully searched for the presence of bacillus tuberculosis and an examination of the lungs should be made by some competent chest man, which examination should include Roentgen-ray study.

Skin tests with bacterial proteins are left on about thirty minutes and then washed off with sterile water and if any of them appear suspicious in comparison with normal controls, notation is made to that effect. The patient is then requested to return the next day for inspection, to see if there are any delayed reactions, being instructed not to irritate the tests any more than is necessary in the meantime. These delayed reactions appear about the site of the scratch tests and are red, inflamed, swollen, hot, tender or even painful, having all the appearances of a mild infection. Occasionally a sterile pustule forms at the site of the scratch. A reaction $\frac{1}{2}$ inch in diameter I call a + 1 (+), a reaction 1 inch in diameter a + 2 (++), etc.

In my experience I do not remember a single case where tests with stock bacterial proteins gave a definitely positive immediate reaction, manifested by an urticarial wheal with pseudopods, such as described by Walker and others. Delayed reactions to stock bacterial proteins on the other hand do occur, and although relatively infrequent, they are of considerable diagnostic importance, which to my mind justifies testing with the bacterial proteins.

Staphylococcus pyogenes aureus, Streptococcus hemolyticus and Staphylococcus albus have been the most frequent reactors in my hands.

Blood Tests. Blood tests are of considerable help in the diagnosis of asthma. Where the leukocyte count is above 10,000 and the polymorphonuclears are around 80 per cent or more, a diligent search for some focal infection is indicated. Where there is a relative increase of lymphocytes at the expense of the polymorphonuclears, it is suggestive of three things: (1) Tuberculosis; (2) lues, and (3) latent streptococcus infection, which should of course be ruled out in the individual case. A Wassermann test should be made on all patients who give a suspicious history, such as repeated miscarriages, and so forth. A Wassermann test should also be made in all cases of continuous asthma, as lues is *something we have to think of in all chronic, undiagnosed conditions.* For example, I have had two patients with continuous asthma who gave positive Wassermann reactions and were almost immediately relieved of their asthma on antiluetic treatment. Both of these patients had an aortic aneurysm.

Some writers have maintained that eosinophilia in an asthmatic is practically diagnostic of protein sensitization. I am forced to disagree with them on this point, however, as I have seen definitely protein-sensitive asthmatics who had no eosinophilia whatsoever, either during or between attacks. Furthermore, some of the highest eosinophile percentages with which I have met, have been in nonsensitive or bacterial cases.

In an asthma case, where a complete history and physical examination, blood tests, Roentgen-ray study, and skin tests with foods, animal epidermals, pollens, stock bacterial proteins, orris root, house dust and other miscellaneous substances, fail to reveal any cause for the dyspnea, I assume that I have made a diagnosis by elimination, of bacteria as the cause of the asthma.

Cultures and Vaccines. The patient is given a sterile sputum bottle wrapped in a clean paper towel and told not to open it until ready for use. He is instructed to wait until he has asthma and as the attack is breaking up and he brings up some of the thick mucus that seems to come from down in his lungs, not saliva out of the mouth nor secretion that drains down from the nose, but what is actually coughed up, he is to open the bottle and spit into it, being very careful not to touch the inside of the bottle or the bottom of the stopper with the fingers; then cork it up tightly and take or send it to my bacteriologist as soon as possible. He is told that if he collects it during the night he is to see the bacteriologist the next day, and if in the morning, he is to see him the same day. At this time cultures are also taken from the nasal secretion (anterior and posterior) and from the throat. Immediate smears are examined and plates and subcultures are made on placenta infusion blood

agar, human blood agar, and such other media as may be indicated. From these the various organisms found are isolated in pure culture, and a vaccine is prepared from each containing two billion organisms per cubic centimeter. The vaccines are killed by heat and held several days for sterility tests. They contain no preservative whatsoever, as we feel their use to be unnecessary where the vaccines are to be handled with strict aseptic precautions. Also, preservatives cause reactions at times that are misleading to the physician and may be decidedly unpleasant for the patient. The vaccines are, of course, kept refrigerated. No vaccine is kept more than one year from date of preparation. All our vaccines are put up in 20 cc. rubber-capped glass vials with a removable glass cap containing a pledget of cotton soaked in 5 per cent phenol. A few sterile glass beads are placed in the vaccine container to facilitate shaking.

Intradermal Tests. The patient is tested intradermally with each of his vaccines, using sterile physiological saline, containing a trace of agar, as a control. We include a trace of agar in our control as we felt that our vaccines probably contained a trace from the culture media, and agar might be irritating to some skins, thus giving us a false reaction. Sterile tuberculin syringes and fine needles (26 gauge, $\frac{1}{2}$ inch) are used for making the tests. The needles should be sharp and free from rust or corrosion, as otherwise we unduly traumatize the skin and may leave a dark spot in the skin. Most writers in giving the technic of intradermal testing say to inject some measured quantity of fluid, namely, 0.01 cc., 0.02 cc., 0.05 cc., or 0.1 cc. My experience with tuberculin syringes is that they all leak more or less, after they have been used a while, so even though you start with some definite amount, there is no telling how much enters the skin, as a considerable portion may "backfire" alongside the piston. When fluid is injected intradermally a wheal or blister is formed immediately, and equal quantities of fluid will produce approximately the same sized wheals. In testing bacterial vaccines intradermally, I start with any where from 0.1 cc. to 0.25 cc., depending upon the apparent tightness of my syringe, and inject sufficient to produce a blister approximately $\frac{1}{4}$ inch in diameter. By this method I feel that I have injected an approximately equal quantity of each of the vaccines and the control, and therefore can fairly compare the subsequent reactions. In making intradermal tests with food, animal epidermal, pollen and other extracts, it is only necessary to inject enough fluid to produce a minute wheal, say $\frac{1}{8}$ inch in diameter, but in testing bacterial vaccines where the quantity of allergic material is probably small it seems desirable to me to inject the larger quantities. I have been able to obtain but little diagnostic information from inspection of intradermal bacterial vaccine tests after thirty minutes,

as considerable traumatic inflammation is usually present and furthermore it has not been my experience to see definite urticarial wheals with pseudopods appear. However, if any of the tests have a larger wheal or show more inflammation than the control, notation is made to that effect. The patient is requested to return the next day for inspection of the tests, being instructed not to irritate them any more than is necessary in the meantime. Delayed reactions to intradermal vaccine tests differ only in degree from those obtained with stock bacterial proteins, being much more marked as a rule, and they are charted in the same way, that is, a reaction $\frac{1}{2}$ inch in diameter is called a + 1 (+), and so forth. When the control is also inflamed the diameter of this inflammation must be subtracted from that of the vaccine tests in order to estimate the true size of the bacterial reactions. Positive reactions to intradermal autogenous vaccine tests are just as common as positive reactions to cutaneous tests with stock bacterial proteins are rare. Those vaccines which fail to show a reaction in twenty-four hours are discarded and those which react are used for treatment.

TABLE SHOWING RESULTS OF INTRADERMAL VACCINE TESTS.

Organism.	Number of tests.	Number of positive reactions.	Per cent of positive reactions.
Staphylococcus pyogenes aureus	87	71	82
Streptococcus hemolyticus	79	23	29
Streptococcus viridans (nonhemolyticus)	67	16	24
Staphylococcus pyogenes albus	12	9	75
Pneumococcus	12	3	25
Micrococcus catarrhalis	10	8	80
Bacillus mucosus capsulatus (Friedländer)	9	9	100
Diphtheroid bacillus	7	6	86
Bacillus coli anaërogenes	1	1	100
Bacillus pyocyaneus	1	0	0
Totals	285	146	51

Treatment. If the test reaction was marked the initial dose is 0.025 cc., or 50,000,000 organisms; if the reaction was moderate the first dose is 0.05 cc., or 100,000,000; and if the reaction was very slight or doubtful the first treatment is 0.1 cc., or 200,000,000. If there are two or more vaccines to be given in any one case and the test reactions were nearly equal, an equal dose of each one is drawn into the same syringe and all injected together, the dose of each one being the same as if that were the only one being given. If one vaccine gives a marked test reaction and another vaccine gives a relatively mild reaction, a small dose of the marked reactor is injected in one arm and a larger dose of the mild reactor is given in the other arm. The patient is instructed to look at his arm or

arms the next day, about twenty-four hours after treatment, to see if there is any local reaction, namely, if there is a red spot or not, and, if so, about how large. A red spot twenty-four hours after treatment the size of a dime or larger is called a local reaction. Treatments are given regularly every five to seven days, preferably the latter. The second treatment is usually double the dose of the first, and for each subsequent treatment the dose is increased by the amount of the first treatment, providing a local reaction is obtained each time. It is desirable to obtain a local reaction from every treatment, so if any individual injection fails to give such local reaction, the dose for the next treatment is increased by the amount of the first treatment plus the amount of the previous increase. For example, if the first treatment is 50,000,000, the second would be 100,000,000, the third 150,000,000 and so on, provided a local reaction occurs each time. If the first treatment is 50,000,000 and reacts, and the second treatment of 100,000,000 should not react, the third injection would be 200,000,000 and if this treatment reacted, the fourth would be 300,000,000 and so on. If a marked local reaction, that is, an extremely sore arm, or a constitutional reaction such as a definite aggravation of the asthma should follow any individual treatment, the same dose should be repeated for the next treatment, or it may even be advisable to go back to the previous dose which failed to produce such reaction. Treatments are continued until a maximum dose is reached or until the vaccine is used up. It is my rule never to inject more than 2 cc. of vaccine (4,000,000,000 organisms) in any one arm at one time.

If for one reason or another a patient's treatments are interrupted it becomes necessary to decide what dose to give when he returns. If approximately two weeks have elapsed since the last treatment I repeat the same dose. If approximately three weeks have elapsed, I go back to the dose of the next to the last treatment, and so on. In other words, I take the number of weeks that have elapsed since the last treatment and subtract one, which gives me the number of treatments to count back to arrive at the proper dose. If a patient has been doing nicely on vaccine treatment and later fails to respond to the same treatment, fresh cultures should be taken and vaccines prepared and tested as before, as the patient's flora have probably changed. In certain acute cases of asthmatic bronchitis it seems unwise to wait for the preparation of autogenous vaccines, and a stock, mixed respiratory bacterin is used instead.

Results. One hundred and forty-four cases of asthma have been treated with bacterial vaccines according to the method described in this paper. Of these, 74 cases or 51 per cent were completely relieved of asthma, 56 cases or 39 per cent were improved in varying degrees, and 14 cases or 10 per cent were unimproved. In other words, 90 per cent were completely or partially relieved of their

asthma and in only 10 per cent of the cases was the treatment a failure.

Discussion. The method of diagnosing and treating bacterial asthma as given in the preceding part of this paper has been arrived at by a process of evolution. When I first started to treat asthma, autogenous vaccines were used in all cases which failed to react to skin tests with the proteins of foods, animal epidermals, pollens, and the like. These vaccines were prepared from cultures obtained from the sputum, and in an occasional case where there were definite nasal symptoms, cultures were also taken from the nasal secretion. Whether a dominant organism or a mixture of several organisms was to be used, was left to the judgment of the bacteriologist. Only one type of vaccine was prepared for each case, but in two separate concentrations: 1,000,000,000 organisms per cubic centimeter and 5,000,000,000 per cubic centimeter. Treatment was started with 0.1 cc. of the weaker vaccine, which dose was increased by about 0.1 cc. each time until a dose of 1.cc. was reached, then changed over to the stronger vaccine, starting with about 0.2 cc. and increasing in a similar manner as before until a maximum dose of 5,000,000,000 had been reached. I noted that a number of patients who were entirely free of asthma on the smaller doses, would unexpectedly blow up with asthma on the larger doses of the stronger vaccine, so we compromised on a single concentration of 2,000,000,000 organisms per cubic centimeter. My vaccines were formerly put up in 1-cc. glass ampules, which, although it ensured that the vaccine would remain sterile until used, was very wasteful of vaccine on the smaller doses, and considerably more troublesome to handle than the single, rubber-capped, glass vial. Treatments were originally given twice a week but it seemed that patients did better as a general rule with a weekly interval, especially on the larger doses.

It was observed that in patients who got local reactions from treatments the results were usually good, whereas in patients who got no local reactions the treatments were almost invariably a failure. Cutaneous or scratch tests were found to be of no avail for testing vaccines, undoubtedly due to the fact that the reacting substance is bound up in the bodies of the bacteria. In view of this it was decided to perform an intradermal test with the autogenous vaccine prepared in each case before treatment was started, and if no reaction was obtained from the test, it was thought best to discard the vaccine and obtain new cultures. Where a positive reaction was obtained by the intradermal method to a vaccine containing two or more different types of germs, it was impossible to tell which one was the offending organism. We therefore prepared a dry, powdered protein from every one of the various types of organisms isolated in the individual case, and the patient was

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tested cutaneously with the same. These proteins were extracted with alcohol and ether, after the method described by Walker. The principal obstacle met with was in getting the proteins dry, and as a separate set of proteins had to be prepared for each case, it was quite a job. As the proteins had to be dissolved again in making the tests, it was finally decided not to attempt to dry them at all, so the individual protein extracts were put up in capillary glass tubes with the ends sealed, and labeled, until such time as the tests were to be made. The dry, powdered proteins and the liquid protein extracts were prepared and tested on a very large number of patients, but in only a single instance was a definite positive reaction obtained and that was to the protein of Staphylococcus aureus. In most of these same patients however a vaccine prepared from the same organism as the proteins would give a positive intradermal reaction. It was inferred from this that our laboratory methods of extracting the allergic substance from bacteria were sadly deficient, and as we could get the patient's own tissue cells to do this for us by means of the intradermal vaccine test, why bother with it at all? Therefore, we adopted the method of preparing a separate vaccine from every organism isolated in the individual case, and testing the patient intradermally with the same, interpreting the reactions after twenty-four hours.

Rackemann states that he has found the intradermal method of testing vaccines unsatisfactory for the reason that certain organisms give large local reactions on each and every individual. This has not been my experience in testing the respiratory infection organisms, with the exception of Friedländer bacillus (see table).

Rackemann tests the vaccines by injecting subcutaneously about 500,000,000 organisms of each, interprets the local reactions twenty-four hours later, and selects the vaccines for treatment that react, and discards those that do not. I am opposed to the injection of such large test doses, because of the probability of aggravating the patient's trouble.

Agglutination tests were also performed on a considerable number of cases, using the patient's own blood serum in varying dilutions: 1 to 12½, 1 to 25, 1 to 50 and 1 to 100, against each of his own organisms and also, in most cases, against Staphylococcus aureus obtained from another asthmatic. More or less agglutination of every organism was obtained with a dilution of 1 to 12½, but with a dilution of 1 to 100 agglutination occurred in only one solitary instance. That was with a Staphylococcus aureus and the patient's own serum, and this was the aureus just referred to that was tested against other patients' blood sera. Because of the extremely discouraging results from agglutination tests we discontinued them.

The bacteriological and serological work has been performed by Dr. O. B. Hunter, professor of bacteriology and pathology,

George Washington University Medical School, and I wish to take this opportunity to express my appreciation of his ever willing and able coöperation.

I am fully conscious of the fact that Cooke, Bernton and others maintain that bacteria are never the fundamental cause of asthma, but are merely secondary invaders; that cutaneous tests with stock polyvalent bacterial proteins are useless and unreliable, as reactions seldom occur and when they do are likely to be to some organism that cannot be isolated from the patient; that the use of vaccines is illogical; that it is never possible to shock a patient to the extent of producing an attack of asthma with a bacterial vaccine, as can be done with other types of protein extracts; and that where good results are obtained by the use of bacterial vaccines it is always due to nonspecific action. I am forced to disagree with all of these opinions. If patients can have asthma from becoming sensitive to the proteins contained in foods, animal epidermals, pollens, and so forth, why cannot they also have asthma from becoming sensitive to the proteins contained in the bodies of bacteria? It is true that reactions to cutaneous tests with stock, polyvalent bacterial proteins are seldom obtained, probably due to imperfect methods of extraction, but when they have occurred in my experience have usually been of valuable diagnostic significance. Very rarely a reaction is obtained to some organism that cannot be isolated from the patient but this is nothing against the value of the tests, as we must remember that the organism may be present in some remote part of the body such as the appendix, gall bladder, or intestinal tract, or the reaction may represent a sensitization produced by some previous infection that has ceased to exist, such as a boil, carbuncle or infected tonsils. I have produced an attack of asthma out of a clear sky innumerable times by too large a dose of vaccine. The attack of asthma occurs coincident with the reaction on the arm. If the good results from the use of bacterial vaccines are always due to nonspecific action it would seem that large doses would work better than small ones, but I have repeatedly found the reverse to be the case.

Summary. A detailed description is given of a method of diagnosing and treating bacterial asthma.

One hundred and forty-four cases of asthma have been treated with bacterial vaccines in accordance with the method described, and of these cases, 51 per cent were completely relieved of asthma, 39 per cent were improved in varying degrees, and 10 per cent were unimproved.

The various steps taken by the author in arriving at the present method are briefly outlined.

Certain objections to the use of bacterial vaccines in asthma are referred to and answered.

THE MECHANISM OF THE FLOW OF BILE FROM THE LIVER INTO THE INTESTINES.

Conclusions from Previous Studies.

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and

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The physiology of the gall bladder and biliary passages constitutes a complex problem. In several papers[1, 2, 3, 4] we dealt with various phases of the subject from an experimental point of view. It is our present purpose to integrate the results of these studies and to apply them to a theoretical conception of the mechanisms involved in the flow of bile from the liver into the intestinal tract.

Bile is secreted continuously into the hepatic ducts by the liver. The rate and quantity depend on several factors; for example, much less is secreted during the fasting state. It is generally thought that the liver cells actively secrete bile and the secretory pressure has been estimated as approximately 300 mm. of bile.[5] This is usually measured by placing an upright manometer in the common duct, tying off the latter beyond the cannula and occluding the cystic duct at the same time. It should be pointed out at once, since this has given rise to confusion in the discussions of the problem at hand, that the secretory pressure so measured is the maximum pressure that the liver cells are capable of exerting against an obstruction and not the same as exists in the common duct under normal conditions. Here the liver is secreting into a duct system which includes a distensible gall bladder and a relaxable sphincter of Oddi.

By inserting a *T* cannula in the common duct, instead of blocking it, we found that the pressure in the common duct of the dog during the fasting state and under anesthesia is relatively low. It measured 60 to 70 mm. of bile, with the cystic duct occluded and varied little, only 3 to 6 mm., with respiration. Bürker[6] obtained similar figures for the normal intraductal pressure.

This is considerably less than the resistance which the sphincter of Oddi offers to pressure from the common duct side, which averaged in our series of dogs 120 to 130 mm. of normal saline. Such a tonus figure is probably fairly constant during the fasting state. It is true that we did observe occasionally a spontaneous ooze of a few drops of bile or the escape of a few drops with each inspiration through the sphincter of Oddi into the duodenum during the fasting state. The significance of this, as well as the entire question of the sphincter control, will be discussed later.

We may state, then, that bile is secreted continuously into the hepatic ducts and is present in the common duct under a pressure of 60 to 70 mm. of bile. It meets the closed sphincter of Oddi which presents a resistance of 120 to 130 mm. of saline. Since it cannot distend the rather rigid liver tissue, and since the cystic duct offers only the slight resistance of 30 mm., the bile flows through the cystic duct into the gall bladder. Rous and McMaster found that a pressure of 60 mm. of bile was sufficient to fill the dog's gall bladder through the cystic duct.[7]

The question arises at once as to whether the pressure within the gall bladder permits this inflow. This is dependent on the phase of respiration. During expiration the pressure in the gall bladder is the result of the hug of its elastic, muscular wall on its contents. We have noticed that the gall-bladder wall accommodates itself to its contents. This is probably brought about by a reflex act. The actual pressure within the gall bladder depends on the tonus of its musculature and elastica, and this probably on the inherent irritability of these tissues as well as on the innervation tonus. The tension of the wall about its contents is of great importance, as we shall see later, in permitting the increased intra-abdominal pressure, due chiefly to the inspiratory phase of respiration, to effect a large increase in the intravesical pressure. In our studies we found that the pressure resulting from the tension of the wall averaged the low figure of 35 mm. of bile during expiration. It will be seen at once that this is lower than the pressure in the common duct, so that during expiration bile may flow into the gall bladder. During inspiration a different state exists. As a result of the increased intraäbdominal pressure, the pressure within the gall bladder rises to 100 mm. of bile or slightly over. At this phase bile cannot enter the gall bladder, but must remain in the duct system. Bile from the gall bladder, on the other hand, can be expelled into the common duct through the cystic duct. It does not then enter the duodenum necessarily, since the sphincter tonus, 120 to 130 mm. of saline, is still somewhat greater than the pressure within the gall bladder at inspiration.

There is also another factor to consider here. Either because of the individual anatomical relations or because of respiration, it is possible for a kinking of the cystic duct to be present. In such a case, of course, the increased pressure during inspiration may be ineffectual in driving bile out of the gall bladder. This may be true in a certain number of instances, and thus accounts for individual variations in both filling and emptying of the gall bladder. As a matter of fact, we have observed in our experiments on the color of bile that in the fasting animal dark bile may be present in the common duct as well as in the gall bladder. Furthermore, in our studies we noted fluctuations in the common duct pressure, which were transmitted from the respiratory pressure changes within the gall bladder.

To summarize, we may say that in the fasting state, during expiration, bile enters the common duct, meets the closed sphincter of Oddi, backs up through the cystic duct and enters the gall bladder. At inspiration some bile from the gall bladder is driven into the duct system without entering the duodenum, except for the occasional escapes noted above. Due to the rapid concentrating activity of the gall-bladder mucosa,[7] it seems probable that what leaves the gall bladder represents the considerably larger amount of bile which entered it.

We have found that when the sphincter of Oddi is kept patent by means of a small glass cannula, as described in our studies on the entrance of bile in the duodenum,[3] the gall bladder does not fill. It remains completely collapsed, all of the bile flowing immediately into the duodenum. This demonstrates the importance of the sphincter in the filling of the gall bladder. Such a mechanism as we have described, that is, the liver secreting bile into the ducts, a distensible and concentrating gall bladder to take up the secreted bile, and the pressure factors due to the respiratory act plus the resistance of the sphincter of Oddi, seems to offer a plausible and logical explanation of the filling as well as the emptying of the gall bladder.

It remains now to consider the entrance of bile from the liver and the gall bladder into the duodenum. We have seen that the bile, as it is secreted by the liver into the ducts, meets the resistance of 120 to 130 mm. of saline offered by the sphincter of Oddi and backs up into the gall bladder. There then follows, with the respiratory act, an ebb and flow between the gall bladder and ducts. But we know that occasionally, even in the fasting state, a little bile enters the duodenum, and that during the feeding state a fairly large quantity enters. In fact, as estimated by pigment studies, biliary, common duct and duodenal fistulæ, it is found that 800 to 1000 cc. of bile are produced by the liver daily, and probably most of this in more or less concentrated form enters the duodenum.

It is apparent that the sphincter of Oddi, like the pylorus, is the "keeper of the gate." The factors controlling its tonus seem to be of prime importance in the mechanism of the entrance of the bile into the intestine. We have already presented experimental studies on its control.[2] It seems that the substances present in gastric chyme, such as dilute hydrochloric acid, peptones, dextrose and fat, when placed on the papilla of Vater relax the tonus of the sphincter of Oddi. Twenty-five per cent of magnesium sulphate acts likewise. Furthermore, pilocarpin given subcutaneously increases its tonus, while adrenalin and atropin decreased it. We found no evidence of reciprocal innervation or contrary action between the gall bladder and the sphincter. In fact, pilocarpin increased the tonus of the sphincter and the gall-bladder wall

simultaneously, while atropin and adrenalin relaxed the tonus of both. It was further found that substances which relax the sphincter of Oddi locally, particularly 25 per cent of magnesium sulphate, did not change the pressure within the gall bladder, although they lowered the tonus of the sphincter. Moreover, increasing the pressure in the gall bladder had no effect on the tonus of the sphincter of Oddi. It seems probable that the stimulation of the vagus nerve excites the gall-bladder musculature as well as the sphincter of Oddi, and the sympathetic nerve inhibits both. We do not know how substances act locally to relax the sphincter, but the fact is beyond doubt.

At this point one observation deserves emphasis. In these experiments the tonus of the spincter was only reduced one-fifth or one-sixth below the original figure. In any case it did not go below 90 mm. of saline. While it is obvious that the sphincter must be opened in order to allow the entrance of bile into the duodenum, yet this is not in the nature of a complete relaxation or loss of tonus. The failure to distinguish between a lessening of the resistance of the sphincter by a moderate decrease in its tonus and a complete loss of tonus with a widely opened sphincter has caused confusion in the discussion of the problem. It has been suggested that with the sphincter open practically no pressure is necessary, and that the bile from the gall bladder and liver merely flow by gravity or slightly aided by muscular and intra-abdominal pressure into the duodenum. It seems probable, however, that like other sphincters in the gastrointestinal tract, the sphincter of Oddi maintains its tonus and that certain nervous and chemical stimuli decrease it somewhat. The tonus is not, however, completely lost under normal conditions. It may seem, moreover, from our studies that a pressure of 90 mm. of saline at least is necessary to overcome the sphincter, even when its tonus is decreased by substances acting either locally or through the vegetative nervous system.

When the sphincter is not relaxed, and presents the usual tonus of 120 to 130 mm., the pressures prevailing normally in the common duct (60 to 70 mm. of bile) and in the gall bladder (35 mm. from the tensity of its wall and 100 mm. or slightly over at the end of inspiration) are insufficient to overcome it. Of course, it is possible, under conditions of greatly increased intraäbdominal pressure (vomiting or coughing), that even the tonus of the unrelaxed sphincter may be overcome and bile thus enter the intestine. To repeat, then, when the sphincter of Oddi is partly relaxed a pressure of 90 mm. or over seems necessary to overcome it. What provides this pressure?

We have already pointed out that the usual pressure in the common duct, as distinguished from the maximum secretory pressure of the liver, is quite low—60 to 70 mm. of bile. If we

assume that this is the usual pressure, then it seems as if during expiration, even when the sphincter of Oddi is relaxed, the bile secreted into the common duct by the liver cannot enter the duodenum. At inspiration, however, the pressure in the gall-bladder rises to 100 mm. or over, and this is sufficient to drive some bile from the gall bladder and common duct into the duodenum.

An objection may be raised at once to the belief that the gall bladder is necessary to drive even the liver bile into the duodenum. It may be asked how the bile gets into the duodenum after cholecystectomy. In answer, it may be stated that several observers (such as, Rost, Judd and Mann,[9, 10]) have found that after excision of the gall bladder the ducts dilate widely if the sphincter retains its tonus and thus act as a gall bladder, or the sphincter loses its tonus almost completely, very little pressure sufficing to overcome it. We have also observed in some studies on the sphincter tonus in the same animal, before and after cholecystectomy, that the ducts may dilate and the sphincter lose its tonus as well. Mann[11] found that the sphincter tonus was only 30 mm. in species without a gall bladder.

The above description of the manner of the entrance of the bile into the duodenum may be summarized by stating that under the local relaxing effect of the gastric chyme, and probably also reflexly through the vegetative nervous system, the tonus of the sphincter of Oddi is reduced sufficiently so that the rise in pressure in the gall bladder and common duct during inspiration opens the sphincter, and bile from the gall bladder and liver flows into the duodenum.

Our experimental studies give much support to this description of the mechanics of the biliary outflow system.

Although many forms of local, general and reflex stimuli were separately applied to the anesthetized operated animal, a gross contractile emptying of the gall bladder was never observed. In the roentgenographic studies of Winkelstein[12] and Abramson[13] contractile motions of the gall-bladder outline were not seen. It seems probable that the function of the elastic wall of the gall bladder is to accommodate that organ to its changing content. This maintains a moderate degree of intravesical pressure which possibly renders the inspiratory squeeze more effectual.

We had experimental evidence that a definite dyed specimen of bile may entirely leave the gall bladder of a healthy animal in twenty-four to fifty hours. Since contractile emptying had not been observed, and since bile did leave the gall bladder to enter the duodenum, another explanation had to be sought. On several occasions during the fasting state bile was observed to enter the duodenum at each inspiration. Also in the experiments in which the sphincter of Oddi was kept patent, dyed bile from the gall bladder entered the duodenum with each inspiration. In the fluoroscopic studies already mentioned compression of the gall bladder

in a craniocaudal direction could be seen at each inspiration. Furthermore, the studies on the pressure variations in different parts of the biliary tract demonstrated the comparatively great fluctuations in intravesical pressure produced by the respiratory act. Apparently the relations are so nicely adjusted that when the sphincter is unrelaxed bile flows into the gall bladder because the inspiratory act is not sufficient to overcome the sphincter's resistance, but when the sphincter is properly relaxed the pressure in the gall bladder due to inspiration is adequate to drive bile into the duodenum.

Most experimenters in this field have assumed that increased abdominal pressure operates equally throughout the abdomen and is, therefore, not of importance. They have not realized, as our pressure studies show clearly, that the same factor acting on different structures produces different pressure changes within them, depending chiefly on their size, shape, outlets, wall and contents. A pressure which produces a large fluctuation in the gall bladder, for example, effects less change in the duodenum and almost none in the common duct. Certainly, mechanical forces as well as neuromuscular arrangement and action play a large role in the physiology of the abdomen.

An interesting illustration of the mechanism which we have described above occurred in one of the experiments performed by McMaster and Rous in their studies on the total bile.[8] After tying off the cystic duct they connected a tube from the common duct to a toy balloon. From the further end of the balloon they led a tube out through the lateral abdominal wall. "Once in every twenty-four hours the outlet tube was opened. The intraäbdominal pressure caused the bile to gush forth rapidly and emptied the thin-walled balloon completely, proven by the failure to obtain more bile by aspiration and by washing the balloon with sterile salt solution." Substitute the gall bladder for the balloon, the ducts for the tubing and relax the sphincter of Oddi instead of opening the outlet tube, and you have an analogous mechanism. The lack of rapid complete emptying in the human gall bladder may be explained by the intermittent opening of the sphincter of Oddi.

Although our theory need not necessarily be correct merely because it explains phenomena, yet, since we have adduced some experimental and theoretical evidence in its favor, it is interesting to apply it. What happens during the fasting state and after meals is perhaps obvious from the preceding exposition. Most interesting is the possible explanation of the Meltzer-Lyon test. In this, after the instillation of a 25 per cent magnesium sulphate into the duodenum, bile-stained fluid is obtained, which is at first light yellow in color and then dark brown and then light yellow again. According to Lyon[14] the dark specimen is from the

gall bladder, and is thought to be discharged into the duodenum by a contraction of the gall bladder following a relaxation of the sphincter of Oddi.

With reference to the active expulsion of the gall-bladder bile, our experimental work indicates that the reciprocal action described by Meltzer[15] does not exist, but rather that the magnesium sulphate relaxes the sphincter of Oddi and that then the intraäbdominal pressure squeezes the bile from the gall bladder and ducts through the sphincter into the duodenum.

One important point in the Meltzer-Lyon method of studying gall bladder disease, namely, that the dark bile comes from the gall bladder and that its absence signifies an occlusion of the cystic duct, we can substantiate experimentally in normal animals. In our studies on the color of the bile,[4] liver bile, liver and gall bladder bile and duodenal bile were studied simultaneously by placing cannulæ separately in a hepatic duct and the common duct and a tube through a stomach fistula into the duodenum. We found in the fasting state the bile from the liver was invariably light yellow. In the common duct (from the gall bladder and liver) it varied from a dark greenish brown to a dark brown or tarry, while the duodenal contents, due chiefly to dilution factors, imperfectly imitated the common duct contents. Later the same animals were cholecystectomized and only light-yellow bile was obtained thereafter. It is apparent, therefore, that the gall bladder is the cause and source of the dark bile. In general, it may be said, although the theoretical basis of the test does not appear sound in the light of our experiments, the Meltzer-Lyon is essentially correct in practice.

Summary. The liver secretes bile continuously into its ducts. The sphincter of Oddi then acts as "keeper of the gate," for when it is unrelaxed it offers a sufficient resistance to shunt the bile into the gall bladder. This is made possible by the fact that the pressure within the gall bladder is lower during expiration than the pressure existing normally in the common duct.

At inspiration, with the sphincter still unrelaxed, the increased intraäbdominal pressure raises the pressure in the gall bladder and some vesical bile (if there is no kinking at the cystic duct) flows into the common duct. There takes place then an ebb and flow of bile between gall bladder and common duct when the sphincter is closed.

When the sphincter of Oddi is somewhat relaxed by the gastric chyme or innervation changes the intraäbdominal pressure at inspiration apparently squeezes bile from the gall bladder into the duodenum.

Neither a reciprocal action between the sphincter of Oddi and gall bladder nor sufficient contractile power of its musculature to empty the gall bladder was found in our experiments.

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STUDIES ON THE BLOOD PRESSURE LOWERING PRINCIPLE IN THE SEED OF THE WATERMELON (CUCURBITA CITRULLUS).

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With the abrupt onset of feverishness, pain over the bladder, frequency of micturition, the first thought to enter the mind of a good country housewife was "bladder trouble," and according to a time-honored custom, she immediately procured some watermelon seed, dried them, crushed them, and made a "tea" to offer the patient, not so much as a beverage, but for what she believed to be a specific remedy for the ailment. After a few doses of this, there was a rapid abatement of the symptoms of acute cystitis. Clinicians of the older school frequently prescribed this infusion and claimed success.

With this historical background, it was decided to make a study to discover, if possible, what active substance, if any, in the seed produced the result.

Analyses failed to reveal any alkaloid as the active principle, and attention was directed to the possible presence of glucosides or saponins.

Five hundred grams of the seed were reduced to about a No. 30 powder. This was then macerated for twelve hours with 1500 mils of distilled water which had been rendered slightly alkaline with ammonium hydroxid and previously heated to 60° C. This brownish-yellow infusion was then strained through cheesecloth or gauze

and was filtered several times until very clear. It was then concentrated over the waterbath to the viscosity of a thin syrup, the water in the outer vessel being allowed to boil during the whole process of evaporation. Powdered lead subacetate was added to the concentrated infusion and with vigorous and constant stirring a copious, curdy, yellowish precipitate formed quickly. This was done to precipitate the organic matter containing the glucoside or saponin. The residue was then filtered and washed several times with distilled water. Hydrogen sulphid was vigorously bubbled through this precipitate until it had been decomposed as much as possible. This step was for the purpose of freeing any of the substance in question that may have been caught in the precipitated organic matter and to remove the lead from the preparation. It was then strained through gauze and filtered. Next the filtrate was concentrated to one-half the volume and filtered again until very clear. A little of the lead sulphid settled out and the preparation was rendered free of lead by filtering while hot. Hydrogen sulphid was again bubbled through for a few minutes to make sure there was no lead left in the infusion. It was found well to filter this again as the preparation was not perfectly clear. Equal parts of ethyl ether and dehydrated ethyl alcohol were mixed and added in excess to the clear solution mentioned above. This resulted in a finely divided, creamy-white precipitate. The precipitated drug was allowed to settle completely after which the clear supernatant fluid was poured off. The precipitate was dried on a waterbath over a low flame, and this dried substance was the material to be tested. A little was dissolved in distilled water and its soapy appearance in this solvent directed our attention to the saponin group at once, and tests were carried out as follows:

Five milligrams of the drug were sprinkled into 5 mils of concentrated sulphuric acid. The result of the oxidation was first a yellowish color, which rapidly changed to a bright red, and this in turn, rapidly gave a light brown color, and then a brownish-black. Many saponins are said to give this reaction with concentrated sulphuric acid.

To each of two dry test tubes was added 5 mils of 0.9 per cent solution of sodium chloride. Then were added to each tube, 10 drops of defibrinated sheep's blood. Five milligrams of the drug were added to Tube A; Tube B was used as a control, and received none of the drug. Both tubes were allowed to stand at room temperature for twenty minutes. At the end of this time, there was a definite change of color in the blood of Tube A, from bright red to a light chocolate-brown, and gradually a brownish sediment settled to the bottom of the tube. A slight degree of hemolysis also occurred. However, the blood in Tube B remained unchanged, thus demonstrating the laking and precipitating action of the drug on the cellular constituents of the blood. This, it will be remem-

bered, is a peculiar property of the saponins and agglutinins which occur in many seeds. After the observation, both tubes were placed in a refrigerator together. Twelve hours later, the blood in the control tube had hemolysed completely, whereas, Tube A contained a dark brown sediment and a lesser degree of hemolysis.

Glucosides, it will be recalled, are neutral principles, consisting of glucose combined with some other substance. A certain class of glucosides have the property of foaming when shaken in aqueous solution, and have received the name of saponins, because of their soapy appearance when treated in this manner. As we strongly suspected that such a body was the active principle, it was decided to test for the glucose molecule in the drug as follows: Five milligrams of the drug were dissolved in 3 mils of distilled water in each of 2 test tubes. To Tube 1 were added 2 drops of dilute hydrochloric acid. Tube 2 received none of the acid. Both tubes were placed in a beaker containing vigorously boiling water and allowed to remain for fifteen minutes. About 5 mils of Benedict's solution were added to each test tube after having neutralized the acid in Tube 1, and both were returned to the boiling waterbath. In Tube 1, there was a definite deposit of the red cuprous oxid on the sides and bottom of the tubes, whereas, the control Tube 2 gave a negative sugar reduction test with Benedict's solution. The hydrolysis test was repeated, and the same result obtained.

A little of the drug was added to a solution of potassium ferricyanid containing a slight trace of ferric chloride, and warmed. There was a dark precipitate of Turnbull's blue. This is another positive test for glucosides. These reactions are due to the reducing properties of glucose.

To decide the lethal dose of this substance, a rabbit weighing 2100 gm. was given intravenously 4 mg. per kilo of body weight, or 8.4 mg. (0.004 per cent of its total body weight). This was dissolved in 2 mils of saline solution. There were no remarkable effects of the drug, and the animal continued well. However, some days later, the same rabbit, weighing the same as before, received 10 mg. per kilo of body weight, or 21 mg. (0.01 per cent of the total body weight); yet nothing of interest was observed.

Thus failing to cause any toxic effects with such small quantities, the dose was raised gradually on different rabbits, and the lethal dose was found to be 208 mg. per kilo of body weight, or 499.2 mg. (0.208 per cent of the total body weight) which was 2400 gm. In about three minutes after the injection, the animal seemed quite sick and drowsy and respiration was labored. In five minutes it was seen to crouch on the floor, and would not move when jostled. The pupils were more dilated than normal and reacted rather sluggishly to light. After these observations had been made, the animal was returned to its cage. Forty-five minutes after the injection it seemed much sicker. In an hour and a half after the dose, the

rabbit was dead, and rigor mortis was generalized. An autopsy was performed immediately, and the findings were as follows:

In the examination of the eyes, the right pupil was found to be constricted; the left was apparently normal in size. The lungs were both very congested, two or three dark hemorrhagic areas being seen near the left base. There was no embolism of the coronary arteries, no postmortem clot and the oxygenated blood was darker than normal and somewhat resembled the venous blood. The liver was quite dark, spongy and hemorrhagic. The left kidney was slightly larger than the right and much darker in color, suggesting congestion or perhaps hemorrhage. There were no macroscopic findings in the spleen. The pancreas was also macroscopically negative, as was the gastrointestinal tract. The peritoneum was likewise negative. The bladder was of a purplish color and the vessels of the wall were markedly dilated. The neck of the bladder was ligated, the viscus excised and then punctured. About 25 mils of amber-colored urine was collected. It was found to contain numerous globules of a yellowish, frog-spawn-like substance which was evidently fresh mucus. This is strongly indicative of a specific action on the cystic bloodvessels and epithelium. The albumin test was strongly positive according to the heat-acetic acid method. The macroscopic findings in the lungs and liver seem to substantiate the belief that the drug is a capillary poison in toxic doses. These organs, it will be recalled, were found to be very markedly congested, even to the presence of several hemorrhagic areas.

The supposed saponin was subjected to the xanthoproteic, biuret and Millon color tests for protein and all three tests proved to be negative. No coagulable protein could be present, as all coagulable material had been removed during the process of extraction.

The dilated bloodvessels of the bladder wall of the rabbit strongly suggested that the drug might have a blood-pressure lowering effect in man, peripherally, by bringing about a dilatation of the blood capillaries and possibly of the arterioles themselves. Accordingly, the subject, aged twenty-five years, weighing 63.99 kilos, took orally 300 mg. (0.00046 per cent of the body weight), of the crude water soluble extract and within forty-five minutes, during which time normal activity was indulged, there was a change in the blood pressure from 125/72, pulse pressure 53, to 105/75, pulse pressure 30. In like manner, with body weight again the same, 20 mg. of the active principle were taken, and this time there was also a change from 119/75, pulse-pressure 44, to 105/75, pulse pressure 30. This lowering became manifest within an hour's time.

Effect on the Human Capillaries. This study was carried out with the Danzer-Hooker[1] microcapillary tonometer. The reading on the manometer scale on two separate occasions was 16 and 16.5 mm. Hg respectively; the arterial blood pressure, using the "Tycos" sphygmomanometer, was 120/80, pulse pressure 40.

Twenty milligrams of cucurbocitrin were taken by the subject in 30 mils of water, orally. Thirty minutes later, the capillary pressure by the method of Danzer and Hooker was found to be 8 and 10 mm. Hg upon two successive readings. An hour later, the blood pressure readings were taken again, and found to be only 90/75, pulse pressure 15. This reading was made with the subject in the sitting posture, after climbing three flights of stairs, and after other normal activity. There were symptoms of intracranial discomfort and drowsiness thirty minutes after the oral dose, but no headache at this time. These symptoms were followed by a dull headache about an hour later, which lasted until the patient fell asleep, about eight hours after the dose was administered.

Effect on the Capillaries of the Frog. The effect on the capillaries of 8 frogs was studied as follows:

In each case of the series 2 frogs were put under a bowl with a piece of absorbent cotton moistened with ether. In five minutes usually, they had become thoroughly anesthetized. One of these received the drug, the other being used as a control in every experiment.

The webs of the feet were immediately placed under microscopes, and invariably the capillaries were found to be tightly constricted. In the majority of the cases studied, they were so constricted, that there was no visible bloodflow whatever, while in a few, the blood corpuscles were seen to make their way with difficulty through these channels. These observations were kept up routinely for ten to fifteen minutes, after which 1 frog received an injection of 8 mg. of the drug dissolved in 1 mil of distilled water. In from ten to forty-five minutes the blood in the treated frogs began to flow quite rapidly. This was usually followed by engorgement and then stasis in the capillary bed under observation. In the control frogs, however, the capillaries usually remained tightly constricted throughout the entire observation of them, so as not to permit any bloodflow whatever, while in 1 or 2 cases, the corpuscles were seen to make their way with difficulty through the capillary network. Stretching and relaxing of the web, as being a source of error, was constantly borne in mind, and having pinned the web on the cardboard, care was taken not to disturb the specimen under any circumstances. After the blood began to flow, following the administration of the drug, several of the frogs were again subjected to ether anesthesia, and in only one instance did the capillaries become tightly constricted again. The bloodflow in the arterioles and venules was also diminished by ether, yet this was not so marked as in the capillaries.

The results on the last 2 frogs are tabulated below. Both were etherized for seven minutes, so as to render them immobile for study.

TABLE I.

Frog No.	Time observed.	Diameter of capillaries in micra before injection.	Diameter of capillaries in micra after injection.	Time injected, and amount.	Remarks.
7	8–8.10 P.M.	9.675	.....	.....	Capillaries constricted. No flow.
				10 mg. at 8.10 P.M.	
	8.15 P.M.	.....	9.675	.....	No change.
	8.25 P.M.	.....	16.125	.....	No bloodflow.
	8.35 P.M.	.....	19.350	.....	Bloodflow rapid. Re-etherized 5 minutes.
	8.45 P.M.	.....	19.352	.....	Result of re-etherization—flow slower.
8	9–9.10 P.M.	No capillaries seen	.....	10 mg. at 9.10 P.M.	No capillaries were at all visible.
	9.15 P.M.	.....	9.675	.....	Capillaries invisible until now.
	9.21 P.M.	.....	12.5775	.....	No bloodflow.
	9.30 P.M.	.....	13.8675	.....	Blood flowing slowly.
	9.35 P.M.	.....	16.225	.....	Blood flowing faster.
	10–10.30 P.M.	.....	22.575	.....	Blood flowing very rapidly.

All frogs survived these experiments in spite of the heavy doses given.

From observations on the capillaries of the human and of the frog, it was thought that there might be a small amount of histamin present in the drug, either in the free or in the combined state. There is not to our knowledge any known chemical test for this violent capillary dilator, and the physiologic test was carried out as follows:

A young virgin guinea pig about three weeks old was anesthetized with ether, and one horn of its bicornual uterus removed through a suprapubic incision. This was immediately immersed in a small beaker containing 50 mils of Ringer's solution, which had been warmed to 40° C. One end of the uterus horn was anchored to the bottom of the beaker with a 10 gm. weight, while the free end was attached by a string to a heart lever. The temperature was kept constant. A kymographic tracing was taken with the drum revolving at slow speed. After five minutes there was no contraction of the strip of uterus. A few drops of a 1 per cent solution of cucurbocitrin were added to the Ringer's solution in the beaker. After ten minutes no contraction occurred. Five milliliters of the same solution were added, and the drum allowed to revolve for five minutes. Still there was no contraction. The drum was stopped. After fifteen minutes it was allowed to run at the same speed. At the end of twenty minutes there was a very, very slight, almost unnoticeable rise of the heart lever, as will be seen in the accom-

panying chart, which was scarcely sufficient to call this a positive test for histamin.

Histamin, as will be recalled, or any other oxytocic, even in a dilution of this magnitude, would have produced a rather marked contraction of the strip of uterine musculature.

Effect on the Blood Pressure of Normal Dogs. There were 11 dogs in this series and a lowering of arterial pressure was obtained in 10 of these. As space will not allow, only two of these original trac-

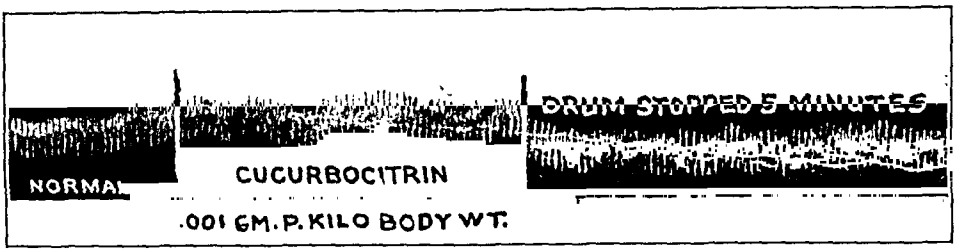


FIG. 1.—Effect of cucurbocitrin (10 mg.) on the blood pressure of a normal dog. Intravenous administration.

ings will be given (see Figs. 1 and 2). These records were routinely obtained with a glass cannula inserted into either the carotid or femoral artery with the dog under ether anesthesia. In one instance, very satisfactory results were obtained with local anesthesia, using a 2 per cent solution of novocain-adrenalin. This was a case in which the femoral artery was used as it did not necessitate the killing of the animal after the operation was finished. All of the dogs whose femoral arteries were used recovered very shortly and healing of these wounds was very rapid indeed. When local anesthesia is used there is some struggling toward the end of the opera-

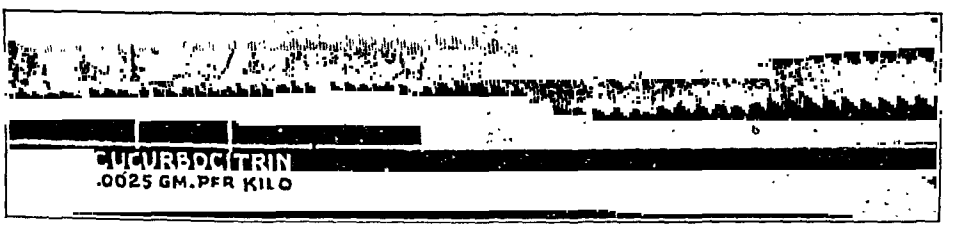


FIG. 2.—Effect of cucurbocitrin (10 mg.) on the blood pressure of a normal dog. Intravenous administration.

tion due to the fact that the dog has to lie in one position for a half hour or more, rather than to pain.

The cucurbocitrin was dissolved in 1 mil of distilled water and injected into the femoral vein each time. It will be noticed from the two charts, that the blood pressure lowering effect was very different from the histamin, nitrite and proteose pepton effects, in that the lowering was gradual, slight, and indeed prolonged, all of which are to be desired when the drug is used therapeutically. The

pressures began to fall in from thirty seconds to three minutes after the administration of the intravenous dose. Again, in spite of the heavy doses received, no ill effects were noticed and all of the animals survived.

It was thought that probably the blood-pressure lowering effect might be due to a depressant or slowing action on the heart. Thereupon, a frog's heart was exposed, and its apex attached to a heart lever for a kymographic tracing. The heart itself was perfused for twenty minutes with a 1 per cent solution of cucurbocitrin, and the drum was allowed to revolve at a moderate rate of speed.

No depressant effect could be noticed, and after ten minutes, there was a slight acceleration of heart beat, due in all probabilities to lessened peripheral resistance through capillary dilatation. This could be readily brought about, as the drug could be absorbed through the serous lining of the peritoneal cavity which was open and accessible to the drug in solution. The kymograph record is given in Fig. 3.

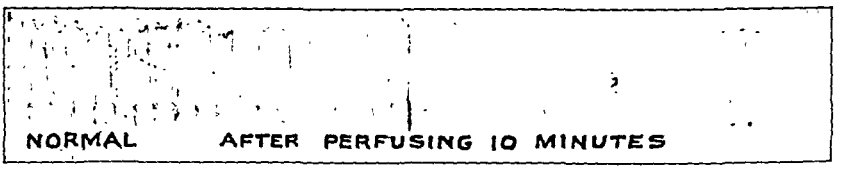


FIG. 3.—Negative effect of perfusing frog's heart with cucurbocitrin.

Effect on Arterial Hypertension in Man. This series consisted of 10 cases of hypertension due to tuberculous nephritis. The 5 cases given in the table which follows are quite typical of the findings in the other patients. The charts of Patient No. 4 are also typical and are submitted as an example. All of the blood pressure readings given are the mean daily readings resulting from two to five determinations. In addition a few arteriosclerotic patients were used and gave very unsatisfactory results, which we cannot explain at the present time. They may be explained by the fact that the blood capillaries themselves undergo sclerotic changes, as do the arterioles and arteries.

Report of Cases. CASE I. M. L., aged twenty-four years, an iron worker, and an ex-soldier, was a heavy cigarette smoker and of a highly excitable nature, had taken strychnin and digitalis for a rapid heart and high blood pressure since his discharge from the army in 1919. He entered the U. S. Veterans' Hospital No. 41, in June, 1922, with a suspected lung lesion, which later was found to be tuberculous. Urinalysis was negative during the first three weeks of his stay in the hospital, but a moderate albuminuria began to appear intermittently after this time; this, in turn disappeared

entirely after a month. Blood pressure readings before treatment remained around 143/70; pulse pressure, 73; pulse rate, 93. This patient left the hospital against medical advice after three months, stating that he felt much better and desired to return to his work.

CASE II.—P. B., aged thirty-three years, a laborer and ex-soldier, entered the U. S. Veterans' Hospital No. 41, on April 7, 1921, with the complaint of a kidney lesion with high blood pressure dating back to 1919. The diagnosis of chronic pulmonary tuberculosis complicated by tuberculous nephritis was made. Before receiving treatment, there was a moderate hypertension of 150/110, pulse pressure 40, pulse rate 48. This patient left the hospital against medical advice in September, 1922.

CASE IV.—R. S., aged thirty-five years, a printer and ex-soldier, entered the hospital about a year previous to this observation, with the diagnosis of chronic pulmonary tuberculosis complicated by a bilateral nephritis. The urinary findings disappeared after a sojourn of about six months in the hospital, only to reappear in May, 1922. By August 16, 1922, however, the urinary picture had cleared up completely, his blood pressure was down to the normal level, and he was subjectively better.

This patient was discharged as an arrested case some time in the spring of 1923.

CASE V.—D. F. K., aged thirty-six years, an insurance agent and ex-soldier, was admitted to the hospital on August 11, 1922, with a questionable pulmonary lesion complicated by nephritis. A minimal lesion was later confirmed at the right apex. There were, also, a double plus albuminuria and hypertension of 155/110, pulse-pressure 45, pulse rate 112. This patient also had evidence of beginning arteriosclerosis. There was a history of active tuberculosis in the apex of the right lung two years previous to his admission to this hospital in 1920, which was thought to have become arrested following conscientious home treatment. He was discharged as an arrested case from U. S. Veterans' Hospital No. 41, some time during the spring of 1923.

CASE VIII.—R. M., aged twenty-eight years, an automobile mechanic and ex-soldier, entered the hospital in August, 1922, for observation as to the cause of his high blood pressure. There was no pulmonary lesion, but his symptoms and urinary findings pointed to a nephritis, probably tuberculous. Initial blood pressure readings were found to be around 135/88, pulse pressure 47, pulse rate 65. This patient was discharged from the hospital some months later, and returned to his work.

The results of treatment are shown in the following table and charts:

TABLE II.—MEAN BLOOD PRESSURE DETERMINATIONS.

Patient, No.	Before treatment.					On treatment.					Remarks.
	Day.	Systolic.	Diastolic.	Pulse pressure.	Pulse rate.	Day.	Systolic.	Diastolic.	Pulse pressure.	Pulse rate.	
1. Age 24	1	143	70	73	93	1	119	50	69	84	Blood pressure within normal limits while drug was being taken.
	2	140	50	90	91	2	137	50	87	82	
	3					8	122	76	46	76	
2. Age 33	1	150	110	40	48	1	132	86	46	59	Three doses administered. Blood pressure within normal limits for three weeks afterward.
	2	135	76	79	62	2	124	75	49	60	
						3	119	59	60	75	
						4	111	51	60	66	
4. Age 35	1	158	105	53	76	1	119	74	45	77	Blood pressure was normal during treatment; duration of blood pressure lowering was about ten days after stopping treatment.
	2	140	95	45	90	2	128	77	51	88	
						3	140	95	45	76	
						9	129	83	46	87	
						10	126	76	50	82	
						11	124	76	48	85	
5. Age 38	1	158	88	70	110	4	131	90	41	93	This patient had beginning arteriosclerosis. Lowering was not manifest until he had been on treatment four days. Blood pressure rose after withdrawal of drug.
	2	155	80	75	112	5	134	92	42	82	
	3	139	95	44	98	6	120	93	27	93	
8. Age 26	1	145	90	55	65	1	124	69	55	72	Blood pressure never ran above normal during the three weeks this patient was under observation.
	2	140	87	53	66	2	119	74	45	68	
						3	139	82	57	84	
						4	124	80	44	82	
						5	120	63	57	76	

Effect of Treatment on Acute Cystitis. Report of a Case. CASE X. —T. P., aged twenty-four years, suffering from chronic pulmonary tuberculosis, was referred to the urologic clinic for the treatment of gonorrheal urethritis. The routine treatment with acriflavine and mercurochrome was instituted. Two weeks later he com-

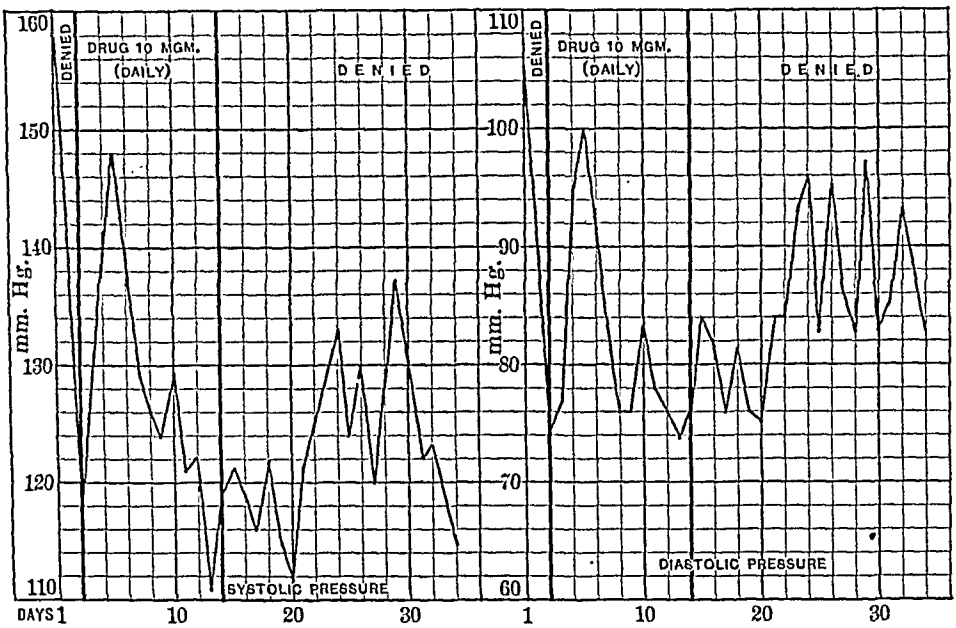


FIG. 4.—R. S. (Case IV). Daily blood-pressure readings.

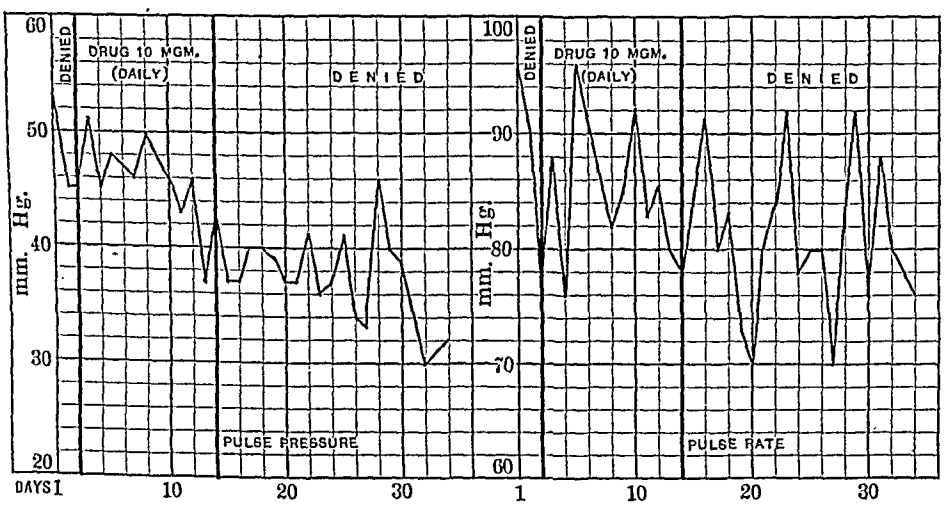


FIG. 5.—R. S. (Case IV). Daily mean pulse-pressure and pulse-rate chart.

plained of sharp pains over the bladder and frequency of micturition. There was slight elevation of temperature and pulse rate above that of chronic pulmonary tuberculosis, and a diagnosis of acute gonorrheal cystitis was made from his history and symptoms. The patient's initial blood pressure was 114/85, pulse pressure 29,

and pulse rate 90 on August 10, 1922. With the hopes of bettering his condition, he was directed to take 10 mg. of cucurbocitrin at 10 A.M. and 9 P.M. for five days. The clinical course was as follows:

August 11, 1922. Blood pressure, 105/65; pulse pressure, 65; pulse rate, 100; pains much less severe, though still some frequency.

August 12, 1922. Blood pressure, 112/70; pulse pressure, 42; pulse rate, 100; subjective symptoms about the same.

August 13, 1922. No observations on blood pressure, and so-forth; but the patient felt much better.

August 14, 1922. Blood pressure, 110/58; pulse pressure, 52; pulse rate, 96; subjective symptoms were even better.

August 15, 1922. The pain had disappeared completely, although there was still some frequency.

August 16, 1922. Still no pain. Frequency less. There was no recurrence of the above symptoms, only slight frequency persisted. It is quite probable that the increased blood supply to the bladder wall and the stimulating effect on the epithelium by the drug was responsible for the improvement in the cystitis Three other cases of acute cystitis were successfully treated as described above, but will not be reported here as space will not allow.

Discussion and Conclusions. This investigation of what is considered to be the active principle of the seed of cucurbita citrullus, to which the name of cucurbocitrin has been given, is evidently a substance belonging to the glucoside-saponin group manifesting certain pharmacological actions worthy of further study.

There is a historical clinical background for this remedy in the alleviation of symptoms incident to acute cystitis. Its use seems rational in that it produces an increased blood supply to the bladder wall, along with a stimulating effect upon the epithelium lining this viscus.

When both the crude extract and the active principle of the seed were taken orally by a subject a number of times, the outstanding effect was a prompt lowering of blood pressure.

The effect upon the blood pressures of 10 out of 11 normal dogs, the effect upon the capillaries of both frog and man, corroborate the clinical observations, and point to the fact that blood pressure is lowered by capillary dilatation, which, in turn, diminishes the peripheral resistance, thereby relieving the laboring heart of a tremendous load.

Autopsies on rabbits following lethal doses of the active principle showed congestion and hemorrhages of lungs, liver and kidneys, and, an observation that seems to be of particular significance, marked dilatation of the bloodvessels of the bladder wall, with a coincident enormous flow of mucus bathing the cystic mucosa, suggestive of selective action by the drug.

With clinical trials in a limited number of cases of moderately increased blood pressure in the human, we obtained a lowering in

both systolic and diastolic pressures with a corresponding lowering in the pulse pressure in most of the cases studied. The pulse apparently becomes more stable, and the patients experienced greater comfort; some of them were able to tell when the pressure was rising after the drug had been denied for a few days.

In 4 cases of acute cystitis, which were treated with the drug, the clinical relief was very prompt.

Histamin, either in the free or combined state, is no doubt absent from the active principle, as the physiologic test on the virgin guinea-pig uterus was negative.

No attempt has been made in this paper to fully explain the pharmacologic action of the drug, and the paucity of clinical material herewith presented is fully realized. However, further studies are in progress, the results of which will be presented in future papers.

In all of the clinical trials, no ill effects were noticed, and for this reason, the drug cannot be considered toxic even in very large doses. It possesses a rather slow and prolonged action. The results in the presence of pronounced arteriosclerosis seem to be very slight, and at the time we cannot account for this. An insufficient number of cases of senile hypertension is a possibility, and further work on these patients might prove encouraging.

The usefulness of this drug is suggested in cardiorenal conditions, and perhaps the other forms, also to the probable specific relief of acute and chronic pathology of the urinary bladder, in that the bloodvessels of the bladder wall become dilated, thereby increasing the concentration of antibodies to combat the invading organism, and for the increased amount of food and oxygen for subsequent repair at this seat of infection. It will be recalled that wounds of the face have a tendency to heal very quickly due to the rich blood supply of this region.

I am very grateful to the following for their valuable assistance and suggestions: Drs. Oliver T. Osborne, L. B. Kline, Francis B. Johnson, J. H. Cannon, L. H. Prince, Robert Wilson, F. P. Underhill, and George E. Barksdale.

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REVIEWS.

MODERN MEDICINE: ITS THEORY AND PRACTICE. Edited by SIR WILLIAM OSLER, BART, M.D., F.R.S. Third edition, thoroughly revised. Reëdited by THOMAS MCCRAE, M.D., Professor of Medicine in the Jefferson Medical College, Philadelphia. Vol. I. Pp. 845; 58 illustrations. Philadelphia: Lea & Febiger, 1925. Price, $9.00.

A THIRD edition of a "System of Medicine" is indeed a *rara avis*. The publication, then, of this Volume I constitutes an important event in American medical literature and calls for congratulations to publishers, editors and authors. Twelve years have elapsed since the appearance of the second edition, and eighteen since the first, which therefore stands about midway between this volume and Pepper's "System." Such is the rapidity of medical advance that Pepper's "System" had already become of historical interest only when *Modern Medicine* first appeared, and in the same way the need for another edition of the latter was annually becoming more apparent. Nevertheless we are glad that the editors have seen fit to include the author's Introduction on the Evolution of Modern Medicine, which had been omitted from the second edition. Like so many of Osler's writings, it is perennially fresh and starts the reader in the way in which he should go to such good effect that it is well worth its twenty pages. The first volume has been shortened by over two hundred pages by omitting the diseases of doubtful or unknown etiology—still no inconsiderable list—and by a steady though slight condensation of most of the chapters. The "new disease," tularemia, is included and scarlet fever lifted from the ranks of doubtful causation. In future volumes sections on botulism and epidemic encephalitis are promised; diseases of the esophagus will be discussed by men who have observed visually their field of work; insulin and metabolism are to be given especial attention. Evidences of conscientious and successful attempts to bring the subject matter up to the latest date are too numerous to mention, but glances at the footnote references will show how many are from the last decade and even from the last two or three years. It is to be regretted that they are not more numerous, and that so many are incomplete in the bibliographic sense. In the chapter on Influenza, which has necessarily been considerably altered, it is

interesting to note that Lord strongly favors Pfeiffer's bacillus as the causative agent. Only one misprint has been observed thus far: that Marmorek found streptococci in scarlet-fever throats in 1825 (p. 747). E. K.

A LABORATORY GUIDE IN GENERAL ZOÖLOGY. By A. RICHARDS, Professor of Zoölogy, University of Oklahoma. Pp. 149. Philadelphia and New York: Lea & Febiger, 1925. Price, $1.75.

IN a laboratory guide in general zoölogy one does not expect to find a systematic treatment of the subject. The plan must include certain well-recognized pedagogic principles, such as proceeding from the known to the unknown and introducing the subject with an animal large enough to be studied without a microscope.

The laboratory guide before us shows a mature grasp of these principles. This is not strange, because the *Guide* is the result of an evolution through several typewritten editions and then through three privately printed editions, extending over a period of thirteen years.

The plan is original, and consists of three parts: Part I gives the principles of morphology and physiology, beginning with the frog, passing to the protozoa, hydra, earthworm and crayfish. Part II deals with the principles of animal biology. Here such general subjects as cell division, embryology, metabolism, genetics, ecology, taxonomy and distribution are treated. Part III, The Animal Kingdom, includes those phyla not covered in Part I, and so represents a general survey of the animal kingdom.

The *Guide* deals with certain factors in evolution, such as animal distribution, but homology and paleontology, which lend themselves so well to laboratory treatment, are notably absent. Perhaps this can be accounted for by the fact that Oklahoma has an anti-evolution law. The book is well printed and carefully written.

H. C.

TEXTBOOK OF NERVOUS DISEASES. By CHARLES L. DANA, M.D., Professor of Nervous Diseases in Cornell University Medical College. Tenth edition. Pp. 667; 262 illustrations. New York: William Wood & Co., 1925.

THIS book, intended primarily for students and practitioners of medicine, is a short account of the most common diseases of the nervous system. In this edition a chapter on the "History of Neurology,' by Fielding H. Garrison, covering forty pages, is one of the worth-while additions. For the most part the description of the various subjects is well done, but many misprints occur that were

also present in the ninth edition. For example, Fay-Sachs disease instead of Tay-Sachs (p. 424); tender joints instead of tender points (p. 204); ognococcus instead of gonococcus, and so on. The reviewer feels that the word neurosis should not be applied to conditions that have organic lesions and that brachial paralyses and other such conditions should not be classed under the heading of Neuroses of the Motor Spinal Nerves, as is done in this book.

Despite the rather numerous typographic errors, and the rather doubtful correctness of classification alluded to, the book can serve a good purpose by giving students a quick and broad conception of the nervous diseases that are met with in daily practice.

N. W.

EMPYEMA THORACIS. By EVARTS A. GRAHAM, M.D., Professor of Surgery, Washington University, School of Medicine. Pp. 106; 13 illustrations. St. Louis: C. V. Mosby Company, 1925.

THIS volume is a consideration of the principles governing the treatment of empyema. It is based on impressive research on the effect of pneumothorax in animals and cadavers and on clinical experience with the Empyema Commission of the United States Army. A new conception of the pathologic physiology of pneumothorax constitutes the most important part of the study. Clinical treatment of empyema of the hemolytic streptococcus variety, based on this conception, reduced the mortality from this condition enormously.

The exposition of the subject is brief, pleasing and convincing.

W. B.

CLINICAL THERAPEUTICS. By ALFRED MARTINET, M.D., Paris, France, with the collaboration of ten physicians. Authorized English translation from the second revised and enlarged edition, by LOUIS T. DEM. SAJOUS, B.S., M.D., Associate Professor of Experimental Pharmacology, School of Medicine, Temple University; Instructor in Endocrinology, Graduate School of Medicine, University of Pennsylvania, Philadelphia. Pp. 1800; 332 illustrations in two royal octavo volumes. Philadelphia: F. A. Davis Company, 1924.

THE work has four subdivisions: Part I, entitled "Therapeutic Agents," is devoted to a discussion of the mode of action of, indications for and use of drugs, dietary measures, the various types of physiotherapy and psychotherapy. In Part II are described the technics of common therapeutic procedures, such as lumbar puncture, paracentesis of the serous cavities, intravenous injections,

cupping and the like. Part III, called "The Treatment of Symptoms," gives a series of individual symptoms, which are alphabetically arranged, with a discussion of the therapeutic indications. Part IV takes up the treatment of particular diseases.

The work contains a wealth of valuable therapeutic information, but its scope is so broad that it has of necessity become shallow and inadequate in places; for example, diets in the vitamin deficiency diseases. In his introduction the author remarks that the aggregate of therapeusis up to the Nineteenth Century may be summed up as "a pile of rubbish and a handful of jewels," and refers to his difficulty in deciding how much to include. He has erred in the direction of too much rather than too little (for instance, the oral administration of preparations of horse chestnut for varicose veins!), and shown a tendency to the polypharmacy of a generation ago. The American reader will be surprised at the advice of temporizing measures under certain circumstances in acute appendicitis. The work of the translator has been very well done; in many instances his parenthetic additions have brought the original up to date, as in the case of insulin therapy in diabetes. R. K.

THE HISTOLOGY OF THE MORE IMPORTANT HUMAN ENDOCRINE ORGANS AT VARIOUS AGES. By EUGENIA R. A. COOPER, Victoria University of Manchester, England. Pp. 106; 61 illustrations. Oxford: Oxford University Press, 1925.

THIS small book is a study of physiologic variations due to age alone in the anatomy (chiefly microscopic) of the pituitary, thyroid, parathyroid and thymus glands. The study begins with early intrauterine life and ends with old age. The material was necessarily from postmortem subjects, but changes due to disease and postmortem influences were guarded against by careful selection.

The style is lucid; the illustrations well selected and technically very good. The description of age variations should serve a very useful purpose in preventing investigators from attributing such to pathological processes. These changes, however, appear from this work to be usually less important than those occurring from similar causes in the breast. The book seems more important as a contribution to the normal histology of organs inadequately described in the average textbook.

It is to be regretted that a consideration of differences in these endocrines (if any) due to sex was not given to this material. A mention of the number of cases examined in the various age periods would have made the conclusions more convincing.

W. B.

THE LIFE OF SIR WILLIAM OSLER. By HARVEY CUSHING, M.D. Two volumes. Pp. 1413; 43 illustrations. Oxford University Press, 1925.

THE reviewer finds himself under the spell and charm of this man that was Osler. Known to him before only in the *Textbook* and *A Way of Life*, in scattered journal articles, *Æquanimitas* and *An Alabama Student*, and admired as clinician and philosopher, he has become to the reviewer in these pages a living personality to be loved and revered.

Wherein lay Osler's greatness? Many and valuable as were his contributions to medical knowledge, one can point to no outstanding scientific discovery of his that will loom large in medical history. Of his contemporaries, some were equally skilled in the medical art; others were as brilliant as teachers. It was something less tangible, less ponderable than these. It lay rather in the great humanity of the man; in a personality and character that inspired all with whom he came in contact in his many-sided life. But such greatness may be lost in a generation with the passing of those whom the man directly or indirectly influenced, unless some inspired brush can forever fix to canvas the fleeting picture before time and forgetfulness blur and erase its details. The author has admirably succeeded. "Merely the outline for the final portrait," says the author, yet how deftly drawn!

That some minor errors should have crept in was inevitable; it is surprising that they are so few. The reviewer calls attention to the founding of the AMERICAN JOURNAL OF THE MEDICAL SCIENCES in 1820, not in 1827 as stated on page 276.

The work should have a universal interest, a catholic appeal. To students: That they may know him who "made it possible for them to work at the bedside in the wards;" who throughout a long, fruitful life was always the eager student and the "young man's friend." To teachers: Because of the indelible mark he left on medical education and the leading role he played in an important period of medical progress—who was, wherever he went, the "potent ferment," "the angel who stirred the pool." To all physicians: That they may know familiarly the life of one of the greatest physicians of all times, and through him something of the glorious history and tradition of their profession; that they may find a fresh idealism and a new inspiration in his example. To the non-medical reader: For here the story of a wonderful life is charmingly told.

R. K.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Sudden Death Due to Exacerbation of Latent Syphilitic Myocarditis.—The first number of a new journal (*Am. Heart J.*, 1925, 1, 1) devoted to the diseases of the heart has just made its appearance. The purpose of this journal, as outlined by the Editor-in-Chief, Dr. Lewis A. Conner, is twofold: (1) To supply a periodical covering the field of the diseases of the heart and circulation, and (2) to supply an organ for the dissemination of the objects and purposes of the American Heart Association. The future of this new journal promises well, judging from the quality of the material, the close editorial supervision and the excellent mechanical reproduction of material in the first number. It might be of interest to detail briefly the articles that appear in the journal and to comment briefly on each of them, as an indication of the type of material which is presented and the character of the work in general. The first article, by WARTHIN, deals with a hitherto unrecognized cause of sudden death which is characterized by the rapid onset of marked symptoms of cardiac insufficiency in apparently healthy individuals. Death in these cases occurs without evidence of valvular lesion, without the usual history of antecedent disease which produces valvular lesions, but with the history of syphilitic infection, developing in young and middle-aged males and instigated apparently by overexertion and heat. In these cases the author has found present in the myocardium large numbers of spirochetes and polymorphonuclear infiltration and marked edema, which he likens to the "critical reaction" which occurs in experimental syphilis in animals as described by Brown and Pearce. The next article, by LIBMAN, discusses the prognosis in subacute bacterial endocarditis. The author

divides these cases into five different types: (*a*) The unusual, (*b*) bacteria-free, (*c*) transitional, (*d*) mild, and (*e*) recurrent. Each of the different types is discussed rather briefly, and from the study of these several types he draws the conclusion that these cases may exist for a long period of time, may recur, occasionally recover spontaneously and in the course of healing chronic valvular disease is produced. LEVINE and NEWTON bring out some interesting observations on the selection of patients with angina pectoris for sympathectomy. They believe that if the right type of patient is selected, without myocardial weakness and preferably without valvular disease, that much can be done to help a patient by this operation. The next article is an economic discussion of cardiac disease by CARR, and is well worth reading. WILLIUS and HAINES, in a short article report on 162 cases of high-grade myxedema, in which they were unable to find any evidence of cardiovascular disease attributable to the myxedema. BRADBURY and EGGLESTON report a very interesting syndrome occurring in 3 patients in which there was marked lowering of blood pressure as a result of changes in posture. They are unable to explain the mechanism of the production of this change, but suggest that it may be due to some disturbance in functional activity of the vegetative nervous system. WHITE and MEYERS outline a method of classification of cardiac diagnosis, and state that every case should have in the diagnosis three features—cause, structural changes and functional ability of the heart; for example, cardiac enlargement and auricular flutter of unknown cause, able to carry on slightly curtailed activities. KERR and METTIER next discuss the circulation of the heart valves and with India-ink preparations of injections of the valves they show that these structures are vascularly very rich, confirming the embolic conception of endocarditis. MCLEAN'S paper deals with methods of lessening heart disease which could be made official. The concluding paper of this new journal describes a new electrode for clinical experimental electrocardiography, as devised by HERRMANN and WILSON. This new electrode is of value not only in the handling of patients, but has a very definite value as an electrode in experimental work on animals.

SURGERY

UNDER THE CHARGE OF

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The After Results of Operations for Malignant Disease of the Breast.—PERRY (*Brit. Jour. Surg.*, 1925, p. 1339) states that operation has justified itself when it is found that 28 per cent of all cases survive

more than seven years. The most favorable age for operation is the quennium, fifty to fifty-four years, both as regards duration of life and also as regards recurrence being delayed for a more lengthy period. In young patients the prognosis is not so good and recurrences are more likely to occur early. The absence of deposits of carcinoma in the axillary glands improves the prognosis, and it is possible that the microscopic evidence of chronic inflammation suggests an increased resistance to the disease. Medullary carcinoma is not such a fatal disease as it is so frequently considered. Cases showing carcinomatous hyperplasia should be regarded as definitely malignant and a radical operation performed. Papillary cystic and intracystic carcinomata are the least malignant and intraductular carcinoma is only slightly more so. Late recurrences do not occur even as long as fifteen years after operation. This possibility almost precludes the establishment of a cure in malignant disease of the breast. All operations must be thorough and one would be inclined to extend the operation still further by removing the supraclavicular glands. There appears to be no grounds for believing that the lower inner quadrant of the breast is a dangerous area for cancer origin.

Noncarcinomatous Tumors of the Stomach.—MEYER and BRAMS (*Surg., Gynec. and Obst.*, 1925, 41, 311) say that a series of noncarcinomatous tumors of the stomach is reported, consisting of one myofibroma, two polyps, one adenoma *en nappe* and one hypertrophic pyloric stenosis in an adult, and mention is made of certain inflammatory conditions, namely, syphilis of the stomach and inflammatory pancreatitis associated with chronic peptic ulcers. The importance in recognizing these conditions consists of the fact that operation, except in syphilis of the stomach, is the only procedure which can cure the patient. Even syphilis of the stomach may require surgical aid if the symptoms of obstruction are severe, or if marked connective-tissue scar stenosis has developed. The nonmalignant tumors of the stomach, especially the myomata and polyps, may undergo malignant degeneration in a large proportion of the cases and early radical removal is the only logical method to prevent this complication. Polyps and myomata may cause severe or fatal hemorrhage or occlusion of the pylorus or duodenum with alarming symptoms. Recognition of these tumors and prompt surgical treatment may not only cure the conditions, but may also prevent the occurrence of serious complications sometimes caused by benign growths of the stomach.

A Clinical Study of Some Common Anatomic Abnormalities of the Colon.—KENTOR (*Am. J. Roentgenol.*, 1925, 14, 207) states that low cecum is a common congenital anomaly of the colon occurring in 18 per cent of all patients. This anomaly occurs more often in persons of the asthenic habitus and is more common in women. Patients with low ceca show a marked tendency to present certain reflex or toxic symptoms. Most of them vomit and many suffer from headache. The exact nature of this association between low cecum and the symptoms described is not yet clear. Attention is thus invited to the colon as a factor in vomiting a hitherto insufficiently emphasized concept. The presence of low cecum can be diagnosed positively only

by Roentgen examination. Appendectomy is usually performed, but is seldom of benefit in cases of low cecum. Appropriate conservative medical treatment gives relief, a cure in the great majority of cases.

Renal Tuberculosis.—PERSSON (*Ann. Surg.*, 1925, 82, 526) says that his cases show that the frequency of renal tuberculosis in men is almost twice that in women. Hereditary tendency can be traced in 25 per cent of the cases. Almost two-thirds of the cases are patients in the third or fourth decades of their lives. The cases of localization to the right kidney exceed those of the left. Coincident tuberculosis in other organs has, according to the records, been shown in about half of the cases. Bladder irritability has been found as an initial symptom in 74 per cent of the cases, pains in the kidney region in 18 per cent, while serious hematuria was noted in 5 per cent. Absence of albuminuria has been noted in 7 patients. Pyuria has never been absent. Tubercle bacilli have been demonstrated in 85 per cent of the cases. The extent and grade of the bladder tuberculosis seems to have exercised a considerable influence on the final result of the operated cases. In slight ulcerations of the bladder the late mortality has been almost three times greater than when such have been absent. In extensive ulcerations the mortality has been extremely great.

Bladder Neoplasms.—MACKENZIE (*J. Urol.*, 1925, 14, 275) writes that one finds a great diversity of opinion both as to pathology and methods of treatment. There are many classifications of these growths and many ways of dealing with the subject. The majority of primary tumors of the bladder are of course the papillary fibroadenomata and the papillary villous cancers. Besides these, squamous-celled cancers, with epidermization, and cylindrical-celled cancers are at times noted. Of other tumors, fibromyomata sometimes with other connective-tissue additions and large, sometimes papillary nodular-sarcomatous myomata of either smooth or striated muscles occur. Much rarer are the ordinary small round-celled sarcomata, spindle-celled sarcomata and very rarely lymphosarcomata and osteosarcomata. Of these groups the epithelial tumors are most important. Hematuria is the chief complaint in these cases. Frequency of micturition and dysuria follow. Pain in the loin, incontinence, pain in the perineum and genitalia are fairly common associated symptoms. The importance of blood in the urine cannot be overestimated. The examination of the prostate is of equal importance. The age and development of the growth must be definitely settled. Freer and more open surgical methods, even in cases of recurrence, must be followed.

Davis Method for Closed Reduction of Congenital Dislocation of the Hip.—DICKSON (*J. Bone and Joint Surg.*, 1925, 7, 873) says that Dr. G. G. Davis, of Philadelphia, described a method for the reduction of congenital dislocation of the hip, which he named the "push method." It may be considered a combination of the direct and circumduction methods. The results in 24 hips reduced by the Davis method were: 21 out of the 24 were reduced, giving a percentage of 87.5 successful reduction. Of the 21 hips reduced, in 3 the results have not been satisfactory. The author feels that these results as to reduction and

outcome compare favorably with those of other methods of closed reduction. He feels that there is less danger of producing a fracture of the femur than in most of the circumduction methods, as the force is applied to the head of the bone, no leverage action being used. There is a minimal amount of trauma to the soft part by this method. The sooner after the age of two years the hip or hips are reduced, the better are the results. The closed reduction after the age of seven years is difficult and the outcome as a rule far from satisfactory.

A Manometric Study of the Cerebrospinal Fluid in Suspected Spinal Cord Tumors.—STOOKEY and others (*Surg., Gynec. and Obst.*, 1925, 41, 429) state that in suspected spinal cord neoplasms manometric readings of the cerebrospinal fluid through lumbar puncture should be a routine procedure. Manometric studies of the cerebrospinal fluid through lumbar puncture (without cistern puncture) may indicate complete subarachnoid block, incomplete subarachnoid block or the presence of a free unobstructed subarachnoid space. In all patients operated upon in whom the manometric tests indicated complete subarachnoid block some form of spinal cord neoplasm was found. In all patients in whom the manometric tests indicated incomplete subarachnoid block either a spinal-cord neoplasm or some other form of subarachnoid block was found. Negative manometric readings were found in 2 patients having an early symmetrical enlargement of the cord, presumably an intramedullary tumor which, however, did not interfere with the free circulation of the cerebrospinal fluid. In all others exposed the manometric findings were substantiated at operation. Combined lumbar and cistern puncture is indicated when manometric studies through the lumbar puncture alone do not permit of definite conclusions being drawn. In the author's experience combined lumbar and cistern puncture was indicated in only 3 cases out of 50 suspected spinal-cord tumors.

Articular Surfaces in Tuberculous Arthritis.—PHEMISTER (*J. Bone and Joint Surg.*, 1925, 7, 835) claims that in the earliest stage the articular cartilage is usually destroyed most extensively along its free articular surfaces by granulations which overgrow it from the surrounding synovial membrane. In the regions of contact and pressure of articular surfaces surface destruction by granulations does not take place and the cartilage is preserved longest. As the disease progresses subchondral granulations develop which absorb articular cortex and attack the cartilage from beneath. In severe tuberculous arthritis there may be early necrosis and caseation of the overgrowing synovial granulations, so that there is little or no destruction of articular cartilage along its free surface. In this event the destruction of articular cartilage is brought about mainly by subchondral granulations, which do not undergo early necrosis and caseation and do not present the usual histologic picture of tuberculous tissue. The bony involvement along the articular surface may be either primary or secondary. When primary the dead bone may break down, leaving a cavity or may persist and form a sequestrum which has articular cortex and in some instances cartilage preserved on it and is denser than the surrounding living bone, which subsequently atrophies. Secondary involvement

of the bone along the articular surfaces may lead either to destruction of the entire articular cortex by superficial caries or to more or less extensive and deep areas of necrosis at the points of greatest pressure in the joint.

Tumors of the Small Intestines.—Lin (*Arch. Surg.*, 1925, 11, 602) states that the lymphoblastoma is the commonest tumor in the small intestine. Spindle-cell sarcoma of the small intestine has never been observed in the Johns Hopkins Laboratory. Males are more susceptible to all tumors of the small intestines than females. The adenoma occurs in persons under thirty years and carcinoma in those over thirty-five years. The lymphoblastoma may occur at any age, but a large proportion, over 40 per cent, are in children under ten years of age. Carcinoma infiltrates early and gives rise to annular growths. Adenoma does not infiltrate and is usually polypoid. The lymphoblastoma may be either annular, polypoid or fungoid, but the form of the growth in the latter bears no relation to the tumor's malignancy. Carcinoma is usually single, adenoma often multiple. Intussusception frequently accompanies tumors which are polypoid or fungoid, being present with almost all in this series either benign or malignant. Only a small percentage of the annular tumors are thus complicated. Stenosis is the rule in all annular tumors. The adenocarcinoma is always malignant, the adenoma always benign. The lymphoblastoma may be either benign or malignant, and there is no possible way to tell whether a tumor of this nature will recur or not even from careful study of microscopic sections.

PEDIATRICS

UNDER THE CHARGE OF

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Thymus and the Treatment of Its Hyperfunction.—DeBuys, Samuel and Bowie (*J. Am. Med. Assn.*, 1925, 85, 1551) state that up to the present time that they have been unable to arrive at a definite standard as to the size, shape and position of the gland causing symptoms, some patients having all the effects of a hyperfunctioning thymus, and on examination showing only a very slight enlargement, while other cases in this series with marked enlargement of the gland showed no clinical symptoms. The heart shows no relationship in size to the thymus, although usually with a marked thymic enlargement there is an increase in the size of the right side of the heart. In a large percentage of these cases the shadow of the thymus is seen to the right and to the left, with the large finger-like projection overlying the right side of the heart. In treating the choice must be made between radium and Roentgen-ray irradiation. In the application of the rays to children, theoretically the use of radium is preferable, as it can be fixed

firmly in place, and no matter how restless the child may be the rays are constantly directed to the region of the gland. In using radium their method is to use 100 mg. of radium element in 2 mm. of brass filter, separated from the skin by a distance of 5 cm. firmly fixed in place by adhesive plaster reinforced by a binder. The duration of the exposure has varied from eight to twelve hours, depending on the urgency of the case and the size of the thymus, as well as the age and the size of the child. Anterior application has been made as a rule, although in giving a series of three radium exposures the second dose has been applied posteriorly. The interval between applications has usually been from ten days to two weeks, unless the condition of the child is grave. Three applications with no improvement has been the limit of its use. The success has been quite uniform, and rarely have more than three or four applications been necessary. No ill effects were observed. Their Roentgen-ray dosage, which is their method of choice, may seem rather mild, but they seem to get the results. They give one minute exposure, 7 inches gap, 5 ma., 1 mm. of aluminum filter, 10 inches distance; this giving approximately one-tenth of a skin unit. The number of treatments required is determined primarily by the clinical symptoms and to a secondary degree by the size of the thymus, as shown in the roentgenogram. No bad effects have been noted following the treatments. The only difficulty attendant on the Roentgen-ray irradiation of the thymus has been the restlessness of the patient, but it has always been possible in some way to hold the child still for the length of the treatment. The average number of exposures required is from four to five. Out of a total of 623 cases of children irradiated at various ages, from birth to thirty-nine months, 125 cases of thymic enlargement have been observed, which is about 20 per cent. The length of time these cases have been under observation has varied greatly, owing to the difficulty of retaining clinical patients under observation.

Comparison and Interpretation on a Caloric Basis of the Milk Mixtures Used in Infant Feeding.—POWERS (*Am. J. Dis. Child.*, 1925, 30, 453) brings out the following points for emphasis in his study: The dilution of the milk mixtures with water affects the calories per unit of mass, but not the percentage relationships of protein, carbohydrate and fat in the total calories. The addition to milk mixtures of an energy-yielding nutrient affects no only the total calories per unit of mass, but also diminishes the proportional representation in the total calories of the protein, lactose and fat. The magnitude of any food component in a mixture, as expressed by its percentage representation in the total calories, is relatively increased by the removal or reduction of any other food component. On the other hand, an energy-yielding nutrient, if introduced in a ratio fixed with relation to the total constant volume of mixtures made increasingly dilute with water brings about a reduction in the values of the protein, lactose and fat percentages of the total calories. When the multitude of milk mixtures commonly used in infant feedings are reduced to the caloric percentage formulation it is perceived that many of them are essentially alike or identical excepting in concentration, degree of denaturization

by cooking, souring and qualitative differences in protein, carbohydrate, salts and fat. Practically all mixtures may be found in one of seven groups. A great number of mixtures which experience has shown to be particularly successful in feeding infants fall into a majority group which approaches the caloric percentage pattern of the food mixtures in the sweetened condensed milk group; about 60 per cent of the total calories are in whole milk and 40 per cent in added carbohydrate. One-third milk with 5 per cent of added sugar, and somewhat less frequently-used mixtures, have the same caloric percentage configuration of sweetened condensed milk and of whole milk to which 17 per cent of sugar has been added. Human milk, cows' milk, whey, protein milk and skimmed milk are the most important representatives of the other groups. The Czerny-Kleinschmidt and Moro butter-flour mixtures have the same proportions of the total calories in protein, carbohydrate and fat as human milk. It is a striking fact that the vast majority of successful milk mixtures used in infant feeding are unlike human milk, which stands apart from all other foods. The popular artificial mixtures are as unlike human milk as they are unlike unmodified cows' milk.

Light and the Antirachitic Factor.—BLOCK and FABER (*Am. J. Dis. Child.*, 1925, 30, 504) state that the clinical investigations hitherto made on the action of light on rickets are not all entirely sound and straightforward. In many instances the experimental conditions before and during the light treatment were not uniform, so that the possibility arises that other factors than the light have exerted an influence. The same thing applies to the research concerning the action of light in tetany. They have had an accurate measure of the intensity of rickets in the phosphorus determination and of the degree of tetany in the calcium determination so that they felt justified in undertaking an investigation into the effect of light on patients with these diseases. These were made during the autumn and winter seasons, during which there is not much sunlight in their country, and when these conditions do not improve spontaneously. The diet consisted of milk and carbohydrates. It was about the same before, during and after the light treatment, and it was usually the same diet as that of children who were ill. No cod-liver oil preparation was given which might affect the disease. The only change was exposure to the mercury-quartz light every other day, beginning as a rule with five minutes daily. The blood phosphorus and calcium were estimated after eight hours' fasting. They have determined the phosphorus and calcium content of the blood in about fifty children, all of whom exhibited the characteristic clinical signs of rickets or tetany or who had both diseases at the same time. The blood phosphorus was restored to normal under the influence of the quartz light. This effect occurred within a month after a total exposure of about one hundred minutes. How soon the effect begins is not at present known although it surely varies, depending on the severity of the case. These investigations proved that it is the light alone that causes the blood phosphorus to rise and as it remains present in normal amount even when the exposure to the rays has been discontinued after a few exposures, this stable.

condition cannot be due to the fact that the light has contributed or liberated a missing substance, be it phosphorus or a vitamin, because these bodies are constantly used up in growth, and a new supply must therefore be furnished. It is more likely that a depressed function is revived by the action of the light. The majority of investigations have shown that the mercury-quartz light has the same curative value in tetany, the concentration of the blood calcium rising from subnormal to normal as a direct result of the light treatment. In all the cases treated by the authors a marked effect on the blood calcium was observed with an almost instantaneous cure of the disease in less than two weeks. Ultraviolet light thus acts on tetany just as it does in rickets. After a few exposures the amount of calcium in the blood rises to normal, but it cannot be made to exceed this, and even before this has happened all clinical signs of the disease have disappeared. Clinically tetany is soon cured by light treatment, while rickets disappears gradually, which is a natural consequence of the fact that the soft bone tissue requires some time to calcify. It is interesting to note that the blood calcium will remain normal, even if the exposure to the rays is discontinued; in fact when it has started to rise it continues to do so irrespective of whether the child is treated or not.

The Chemical Composition of the Spinal Fluid.—WILCOX, LYTTLE and HEARN (*Am. J. Dis. Child.*, 1925, **30**, 513) found that the normal chlorid content of the spinal fluid is from 690 to 720 mg. per 100 cc. Low values are found in acute and tuberculous meningitis. The relation of spinal-fluid chlorids to blood chlorids is not constant, and a determination of blood chlorids is not necessary or useful in diagnosis. The normal protein content of the spinal fluid is from 30 to 80 mg. per 100 cc. It is increased in acute and chronic inflammations of the brain substance. In certain altered metabolic states accompanying infections of nephritis, some increase in protein can be expected. Spinal-fluid sugar should always be determined in relation to blood sugar. The normal relative value is from 40 to 60 per cent of the blood sugar. High relative values are found consistently in epidemic encephalitis, meningismus, convulsions, acidosis and nephritis, in poliomyelitis of the bulbar type and in a certain number of socalled normal cases. From the variety of cases in which a high relative value is found, it will be seen that this is not a reliable diagnostic point. Low relative values are found in acute and tuberculous meningitis with great regularity, and this is of considerable importance. The character of the toxin at work apparently determines to some extent the degree of general or selective change in chlorid permeability. Chlorids, protein and sugar are likely to vary directly with the acuteness of the infective process. They may bear some constant relationship to the disease itself. A knowledge of spinal fluid chemistry is helpful diagnostically in many conditions of the central nervous system. This is especially true in tuberculous meningitis and somewhat less true in purulent meningitis, encephalitis and polio nyelitis. Calcium and phosphorus in the spinal fluid bear no relationship to their content in the blood or to the clinical picture of the patient.

DERMATOLOGY AND SYPHILIS

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The Eczemas of Bread Bakers and Confectioners.—WHITE (*Brit. J. Dermat. and Syph.*, 1925, 37, 166) concludes from a dozen such eczemas that there is no eruption specific or distinctive of these industries and that they are incidents rather than consequences of the work. In an interesting experimental study upon himself and associates of the effect of the ingredients of flour upon the skin, the author found that salt (3 to 5 per cent in water), calcium phosphate and flour, mixed as a wet paste, produced a cutaneous reaction only if it were *kept* moistened; if applied dry there were no eruptions even after many days' exposure.

Mycosis Fungoides.—WILLS and HADFIELD (*Brit. J. Dermat. and Syph.*, 1925, 37, 113) observed that the premycotic stage in a male, aged thirty-one years, started with a dermatitis compatible with a diagnosis of dermatitis herpetiformis, a similar feature previously reported by Pernet and Pringle. With peculiar periodicity in attacks and remissions, the premycotic stage changed suddenly to the tumor-formation period with enormous development of glandular and skin tumors and the patient died from asphyxia from an ulcerating tumor in the trachea.

The Interpretation of Mycosis Fungoides as a Variety of Lymphosarcoma.—FRASER (*Arch. Dermat. and Syph.*, 1925, 11, 425) reports four cases of mycosis fungoides whose histologic picture he interprets as that of lymphosarcoma arising in the perivascular reticular system of the skin. Thus they are classed in the general group of the malignant hyperplasias of lymphoid tissue which may originate in different parts of the body found in many locations, such as the reticular tissue of the skin, submucous lymphoid tissue, lymph nodes and spleen, and could include the usual designated diseases, such as lymphatic leukemia, Hodgkin's disease, lymphosarcoma and mycosis fungoides.

Abnormalities of Blood-sugar Content in Eczema.—HALDIN-DAVIS and WILLS (*Brit. J. Dermat. and Syph.*, 1925, 37, 364) found in about 66 per cent of 20 cases of eczema (excluding frank diabetics) that there was associated some abnormality in the blood-sugar levels, this consisting either of: (1) Abnormally high blood sugar during starvation or (2) appearance of abnormally high amounts of sugar in the blood soon after the injection of glucose (50 gm.). In many of these the

blood-sugar abnormalities were found when the eczema was widespread and accompanied by edema. Neither drastic nor moderate reduction of carbohydrates aided in producing clinical cures, save in those occasional patients where the consumption of sugar and starchy substances was exceptionally excessive.

Some Observations on the Fractional Method of Gastric Analysis in Diseases of the Skin.—In a series of 100 patients, 50 of which were acne rosacea and the other 50 acute widespread dermatoses, BROWN (*Brit. J. Dermat. and Syph.*, 1925, **37**, 213) performed fractional gastric analysis, and concluded that it is a clinical method of decided value in the investigation of dermatologic conditions, being more accurate than the single one-hour test. His finding of hypochlorhydria as a prevailing condition in rosacea (56 per cent) confirms that of Pyle and Barber (58 per cent), but the hypochlorhydria was not as extreme in degree. In other cases it was noted that hyperchlorhydria prevailed in acute widespread dermatoses. Furthermore, complete achlorhydria or extreme hyperchlorhydria may be present in dermatologic conditions without any gastric symptoms.

Fatal Case of Lupus Erythematosus, with Necropsy.—GIBSON (*Brit. J. Dermat. and Syph.*, 1925, **37**, 232) was unable to find any evidence of tuberculosis at the postmortem examination of a male, aged twenty-nine years, who died from acute lupus erythematosus. The recovery of the streptococcus from the blood during his life is of great interest; after death the only focus of infection found was the tonsils. No cardiac vegetations were found.

Effect of Bismuth on the Wassermann Reaction in Patients Unresponsive to Arsphenamin.—BELDING (*Arch. Dermat. and Syph.*, 1925, **12**, 334) found that a course of bismuth (oil suspension averaging twenty injections over ten weeks of approximately 1.33 gm. of metallic bismuth) reduced the Wassermann antibody in 37 per cent of a series of 35 patients, 10 of whom showed neurologic invasion and 3 vascular syphilis, the rest showing no evidence of activity. All had been treated by arsphenamin and mercury and were considered Wassermann-fast; the reduction under bismuth persisted during at least six months' observation.

GYNECOLOGY

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Inguinal Endometriosis.—In one of his more recent contributions to the interesting subject of endometrial implants, SAMPSON (*Am. J. Obst. and Gynec.*, 1925, **10**, 462) discusses what he calls inguinal endo-

metriosis, which in the past has been called by such names as endometrial tissue in the groin, adenomyoma in the groin and adenomyoma of the round ligament. In the 3 cases of inguinal endometriosis on which his study was based the structure of the endometrial elements was identical with that of those found in the uterine wall resulting from the direct invasion of the myometrium by the mucosa lining the uterine cavity. In all 3 cases the nodule in the groin reacted to menstruation as was indicated by its being tender at that time and also by the presence of cavities filled with blood and blood pigment in its tissues. In the first specimen the nodule was situated just below the external abdominal ring and the round ligament was not observed during the operation. In the second the mass of tissue which had reacted to the endometrial invasion was adherent to the side of the terminal portion of the round ligament, but he was unable to demonstrate the actual invasion of that structure by endometrial tissue, possibly because serial sections were not made. This tissue had evidently primarily developed in structures lateral to the terminal portion of the round ligament. In the third specimen the endometrial tissue occupied the region of a femoral hernia and was densely adherent to the anterior surface of the femoral vein. None of these 3 cases could be classified as a tumor of the round ligament, although the author believes that in all of them the endometrial tissue might have reached the groin through vessels accompanying the round ligament. In the first case peritoneal endometriosis was present. There was an endometrial invasion of the uterine end of the round ligament and the structures about it on the same side as the endometrial tissue in the groin near the distal end of that ligament. In the second case peritoneal endometriosis was also present with an invasion of the broad ligament of the same side as the endometrial tissue in the groin. In the third case gross evidence of peritoneal endometriosis was not present. The pelvic organs were inspected but were not removed. The uterus was slightly enlarged with a small leiomyoma presenting between the layers of the broad ligament of the same side as the endometrial tissue in the groin. The possibility of metastasis through lymph channels or veins reached by the invasion of the uterine wall by its mucosa must be considered in this instance, that is, from a primary uterine endometriosis or from endometrial tissue escaping into uterine vessels during menstruation. A study of the whole subject of pelvic endometriosis suggests that at times metastasis occurs through the lymph vessels and possibly through the veins and that endometrial tissue may reach the groin and other parts of the body through these channels. Future studies will demonstrate the truth or fallacy of this interpretation. The author believes that we are warranted in stating that possibly inguinal endometriosis may be secondary to that in the pelvis and that it may arise from: (1) Metastasis through lymph vessels invaded by endometrial tissue implanted about the uterine end of the round ligament and the broad ligament. (2) A direct extension or metastasis along the round ligament from a peritoneal endometriosis about the abdominal inguinal ring. (3) Metastasis from the direct invasion of the uterus or tube by their mucosa with extension to the superficial lymphatics and veins and also from endometrial tissue escaping into uterine vessels during menstruation. (4) Implantations in a hernial sac.

Removal of Stones from the Lower Ureter by the Vaginal Route.—A decision as to the method of choice for the removal of a stone which is partially or completely obstructing a ureter depends principally upon the location of the stone within the ureter and upon the predilection of the individual operator for one or another type of operation. LOWER (*J. Urol.*, 1925, 14, 113) has found the vaginal route of value not only in multiparous but also in nulliparous women and even when the stone is so high in the pelvic portion of the ureter that its palpation is scarcely possible. It is always advisable to try nonoperative measures and cystoscopic manipulations before attempting operation. The author has used the vaginal route for the removal of ureteral stones successfully in 6 cases, while in 2 others he was not successful because the stone moved up the ureter during the manipulation to a point where it could not be reached through the vaginal opening. The technic of this operation is very simple: The patient is placed in the lithotomy position, the cervix is caught with a curved tenaculum and pulled well to the opposite side, thus pulling down the base of the bladder and the ureter. The stone is palpated and an incision is made through the mucous membrane of the vagina parallel to the ureter. The tip of the index finger is then pushed through this slit and the ureter and stone located. A tenaculum is then placed above the stone, to prevent it from moving up the ureter. By releasing the traction upon the cervix and by gentle traction on the tenaculum on the ureter, the ureter and stone are brought within the opening in the vaginal mucous membrane, at which point the stone can readily be removed through a longitudinal opening. The incision in the ureter is closed with a few fine absorbable sutures and the ureter released. A small cigarette drain is inserted through the vaginal slit and is removed at the end of the second day. If there is no leakage of urine, and there is not likely to be, the patient can leave the hospital three or four days after the operation. The advantages claimed for the method are that it is comparatively simple for removing a stone from a location which is often difficult by other methods; it affords independent drainage, it avoids an external incision and it shortens the period of convalescence.

The Leukocyte Count in Ectopic Gestation.—Anything that can aid in making the diagnosis of ectopic gestation in the doubtful cases is certainly of great value, and in order to determine what information can be derived from the leukocyte count FARRAR (*Surg., Gynec. and Obst.*, 1925, 41, 655) has studied the records of 150 cases of ectopic pregnancy which had been operated upon in the Woman's Hospital in New York City. Summarizing her study, she states that in ectopic gestation the leukocyte count fluctuates according to the amount of fresh blood thrown into the peritoneal cavity and the rate of absorption. It tends to drop quickly to normal as the blood in the peritoneal cavity is absorbed or walled in; 48 per cent of the cases had a normal leukocyte count before operation was performed. The count was normal in 29 cases of unruptured tubal pregnancy in which there was no free blood and in 43 cases of ruptured tubal pregnancy in which the blood was walled in. The leukocyte count was an index to the amount of free blood in the peritoneal cavity and the polymorphonu-

clear count was increased markedly only in cases having fresh blood in the pelvis and increased in direct proportion to the amount of recent blood found at the time of operation. The fluctuating leukocyte count together with the moderate elevation of temperature differentiates ectopic gestation from a purulent salpingitis with its more uniformly high leukocyte count and fluctuating temperature. In cases of ruptured tubal pregnancy the steadily rising leukocyte count indicates active bleeding before the fall in the number of red cells or hemoglobin gives warning of the condition. The leukocyte count to be of diagnostic value must be taken at least daily and in critical cases even hourly and used in conjunction with the history and clinical findings in the case.

RADIOLOGY

UNDER THE CHARGE OF

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Cancer of the Tongue and Mouth.—SIMMONS (*Am. J. Roentgenol. and Radium Therap.*, 1925, 13, 545) gives statistics to show that cancer of the buccal mucosa is very malignant and easily overlooked by the patient and physician. Chronic irritation has a definite relation to the etiology. Syphilis seems closely related to the etiology because different series give from 14 to 40 per cent positive Wassermann reactions in this type of cancer. All these growths are squamous-cell cancers, and clinically are divided into two classes: The papillary type, which is of relatively low malignancy, and the rapidly growing type, metastasising early, and often incurable inside of six weeks. Cancer of the mouth should be grouped according to malignancy when reported by the pathologist. Malignancy varies with the position, as carcinoma of the floor of the mouth is most malignant, while that of the lower jaw, cheek and upper jaw are relatively less so, in the order named. In early stages there are few or no symptoms, and all ulcers not yielding to removal of the cause and ordinary treatment after two weeks should be considered cancer. The author believes that surgery of some form followed by irradiation is the best treatment for these cancers. He divides the treatment into three types: Prophylaxis, such as oral cleanliness, early care of obviously benign growths, and if cancer is present attempt at radical removal, or palliative treatment for those definitely beyond cure. A summary of the methods used at the Massachusetts General and Huntington Hospitals is as follows: Morphin and morphin with atropin are given one and one-half hours and one-half hour respectively before the operation; ether is used for anesthesia by the pharyngeal tube method with the pharynx packed off. All cases receive postoperative Roentgen-ray treatment of glandular areas of the neck. Postoperative Roentgen treatment to the operative site has been abandoned unless at least two weeks has elapsed between treatment and operation, as otherwise the treating is apt to be unsatisfactory. In the inoperable types radium

"seeds" in the growth and Roentgen treatment to the glands of the neck give relief to the patient and prolong life. Out of 53 cases the author cites 30 per cent of cures of cancer of the mouth out of an operability of 65 per cent.

A Brief Review of the Indications and Technical Procedures Employed by the Authors in Treatment of Cancer of the Uterine Cervix and Body.—The vast majority of cervical cancers are epitheliomas, according to BURNAM AND NEILL (*Radiology*, 1925, **5**, 1), while in the body of the uterus adenocarcinoma is the most common. Treatment of these cancers depends on their stage of development, whether to be palliative or curative. In early cancers of the body of the uterus they advise hysterectomy unless there is some definite contraindications to surgery when curative procedures with radium should be instituted, such as up to $2\frac{1}{2}$ gm. hours of intrauterine radiation. In borderline cases they would advise hysterectomy when possible, as efficient radium application is difficult to estimate. However, if surgery is contraindicated 3 gm. hours or more combined with external through-and-through treatment should be palliative only, giving 1 or 2 gm. hours combined with external radiation. The authors see no value in preoperative radiation, but do advise postoperative treatment to begin in four weeks by direct treatment to the vaginal vault and cross-firing over the iliac glands. In cancers of the cervix in early cases they advise surgery with preradiation, although in some cases one or the other method alone is advisable. The preliminary radiation consists of 1 gm. hour in the cervical canal and 1 gm. hour covering the entire cervix. The sooner the operation can follow the better, preferably the next day. Postoperative radiation is not advisable except in recurrences. In borderline cases, when the growth involves the vaginal wall or parametria, but is freely movable, there is probably more general combinations of surgery and radiation indicated than in early cases. Here radiation is given with a flat applicator to the involved portion of the vaginal wall, 1 gm. for thirty minutes to each square inch of surface, applied direct with a filter of 1 mm. of brass and 2 mm. of rubber. If radium alone is given it is for $3\frac{1}{2}$ gm. hours in a single treatment, as a single dose is better than broken doses. As a rule, growth disappears locally. A second treatment is not given except in new development. In the borderline cases of cancer of the cervix where there is some fixation operation is not to be considered. The radiation is the same as in the former group, but in addition a strong emanation point is implanted centrally into the involved parametrium. The authors feel that Roentgen-ray radiation has no place in these cases except as a palliative measure in the more advanced types.

Roentgenography of Hydatid Cysts of the Lung.—HEUSER (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 529) reports a case of hydatid cyst of the lung which was diagnosed by Roentgen ray and operated upon. The diagnosis is not always easy and the prognosis with surgery varies with the location in the lung. Sarcoma of the lung is very similar to a cyst, and about the only difference is that in the roentgenologic examination the cyst appears less dense than the sarcoma. Pleural effusion may complicate a cyst in the lower lobe and then the diagnosis of cyst may be very difficult, but is aided

by change of positions in making the examination. In a second case the author shows how it may be impossible to make a clinical diagnosis of pulmonary cyst and the importance of careful attention to roentgenologic findings. He cites cases also to show how pleurisy may complicate the diagnosis of hydatid cyst, that cysts may complicate tuberculosis and cardiac lesions. After operation the case should be followed by roentgenologic examinations in case new cysts may develop. Cysts of the lung may occur with those of the liver and this should be borne in mind so as to make the examinations from all possible positions.

NEUROLOGY AND PSYCHIATRY

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The Average Sex Life of American Women.—Because of the present inadequacy of sex knowledge, a plan was evolved for coördinating the activities of a number of societies that might contribute materially to this problem. DICKINSON and PIERSON (*J. Am. Med. Assn.*, 1925, 85, 1113) present the first of a series of articles that are to appear on sex problems. In making some investigations on contraceptive measures, the following scientific needs were brought out: "Age at marriage and age at childbirth for American women, duration of reproductive life, fecundity and fertility, findings that point to a diagnosis of sex experiences, exact genital measurements, anatomy of sex act and the bearings of it on health, correlation of pelvic disorders and diseases with sex practices of all kinds." The work of Davis on autoerotic practices in women, published in *Mental Hygiene* (July, 1924, and January, 1925), is reviewed as a preliminary to the article. Two-thirds of these women, of average age thirty-seven years, unmarried, report the practice of masturbation. The average age of beginning masturbation was between eight and nine years, well before puberty. The percentages of those indulging in perverse sex acts is given. Of a group of married women, of average age thirty-eight years, the median age of marriage was twenty-five and seven-tenth years. Two-thirds of these experienced pleasure in sex relations after marriage; one-third showed alteration in feeling thereafter, being about equal as regards gain or loss. One in 20 mentioned reception of information on birth control. One-fourth of them continued masturbation after marriage. Fear of pregnancy was rarely present. The sexual impulses of husbands were estimated to be greater in 62 per cent, less in 3.5 per cent and equal in 31 per cent. Coitus occurred on an average of twice a week in the group. Fig. 1, charts for women of temperate climates; the

average ages of onset of autoeroticism, nine years; onset of menses, fifteen years; age of marriage, twenty-four years; menopause, forty-nine years. Average clitoris measurements are given in Fig. 3. To the conventional classification of vaginal orifices: (1) Intact unentered hymen (virgin); (2) married nullipara (wife or cohabiting imparous single women; (3) parous women; the authors add (4) nulliparous orifice of very vigorous coitus; (5) the virgin orifice massaged to various dimensions, some among the largest; (6) the parous orifice that seems to owe its immunity from hymen damage or tear of pelvic floor to the oft-repeated stretch of one or both foregoing experiences. Measurements were made with glass balls of varying size inserted, or with various test tubes or glass cylinders inserted. A chart is given showing various measurements in centimeters. Much stress is placed on palpation of the sharp edge of the hymen. A large percentage (73) of Davis's group approved of contraceptive measures and practised them. These unions averaged 1.9 children and 2.5 pregnancies each. Figures for true sterility are not definite, but it is the opinion they are high. The authors are attempting to study the methods of birth control in foreign countries.

Comments on the Pathology of Dementia Precox.—The lack of uniformity of concept about dementia precox makes it difficult for pathologists and clinicians to agree on findings. Schizophrenia refers to the mental mechanism of some cases, and is sometimes used synonymously with dementia precox. LEWIS (*J. Nerv. and Ment. Dis.*, 1925, **62**, 225) quotes Child concerning the old problem of organic and functional: "The relation between structure and function in the organism is similar in character to the relation between the river as an energetic process and its banks and channel." Literature is cited dealing with findings of the brain and endocrine organs in dementia precox and with the most common clinical findings. The author reviews nine old cases of dementia precox that came to autopsy. Meager clinical material is assembled. The cases showed gradual deterioration, usually from youth. Most of the reports were concerned with autopsy findings. Small hearts and hypoplastic aortas were the rule. Several patients had severe pulmonary tuberculosis. Some compensatory changes had occurred in the endocrine organs in a few. These are discussed. The frequency of pulmonary tuberculosis in dementia precox is explained by the theory of Rokitansky, who believed that valvular disease of the right side of the heart tended to favor the development of chronic phthisis. On the other hand, patients suffering from valvular disease of the left side of the heart are not prone to have pulmonary phthisis. Whether the small heart found in patients with pulmonary tuberculosis is primary or secondary to the disease is open to question. The author feels that in dementia precox the small heart is primary and tuberculosis of the lungs is secondary to the hypoplastic heart and aorta. From a biochemical standpoint literature is cited to show that decrease in blood uric acid in dementia precox has been found but not constantly. Catatonic cases show some tendency to increased blood sugar. The average variability of blood chemistry is greater than in normal persons, showing probably a labile metabolism. It is felt, but is by no means certain, that hypoöxidative processes are

predominant. This bears out work in which basal metabolism was below normal in 50 per cent. A Russian neurochemist has isolated many enzymes from the gray matter of brains of normal people. This opens up new fields. Treatment is reviewed. Where malarial treatment, as for paresis, has been tried no lasting results were obtained. General reëducational and hygienic measures are recommended, including physiotherapy, occupational therapy, etc. Sterile meningitis from intraspinous injection of inactivated horse serum has been induced with apparent improvement in a few cases. The Steinach rejuvenation operation has been tried with negative results. Narcosis induced over several days by special drugs has been reported by European investigators. This method has not been used in America. As yet it has not been given adequate trial. Psychoanalysis is attempted with varying results. The writer seems to lean to the view that true dementia precox is an organic condition intimately associated with hypoplasia of heart and aorta. The hope for treatment, if any, lies in childhood. An excellent bibliography is appended.

Cerebrospinal Fluid Pressure from the Clinical Point of View.—AYER (*Arch. Neurol. and Psychiat.*, 1925, 14, 440) makes a plea for accurate manometer readings of spinal fluid pressure with every lumbar puncture. He prefers the aqueous manometer used with a three-way stopcock interposed between the needle and the manometer. Two lengths of 350 mm. each should be available. The mercury U tube has one advantage in that negative pressures may be read with it. The estimation of drops of fluid per minute or spurt of fluid are to be condemned as unreliable for telling fluid pressure. Normal fluid pressure from the lumbar sac varies between 100 and 200 mm. of water. He regards pressures from 200 to 250 as suspicious and 250 to 300 definitely abnormal. Such pressures are taken with the patient lying on side with head in alignment. In this position cisterna magna and ventricle pressures are the same as lumbar pressures. In sitting posture the lumbar pressure is about doubled, while cisterna magna and ventricle pressures are negative. Holding breath, sneezing, grunting and cramped position tend to elevate the pressures. A feeling of faintness is usually accompanied by lowering of pressure. Compression of jugular veins—Quechenstedt's sign—causes an increase in the pressure unless there is more or less complete occlusion of the subarachnoid space. In very low pressures and when the neck was compressed enough to interfere to cause the patient to cough the author failed to get the usual jugular response and mentions these as sources of possible error. The latter gave an apparent jugular response in a cord-tumor case. A failure of response to compression of a jugular on one side in the absence of possible cord tumor might indicate a lateral sinus thrombosis on the same side. There is no marked correlation between spinal fluid pressure and blood pressure, but the tendency is for a higher fluid pressure in hypertension. Factors that affect the spinal fluid pressure are: (1) "Elasticity of dura mater; (2) intracranial arterial pressure; (3) intracranial venous pressure; (4) secretion pressure of cerebrospinal fluid; (5) rate of absorption of fluid; (6) brain bulk or amount of solid substance in the cranium; (7) hydrostatic pressure provided the patient is in any position other than the

horizontal." Highest pressures even up to 1000 mm. of water, may be seen in acute meningitis brain tumors hydrocephalus and hemorrhage. High pressures may also be seen in uremia polycythemia, cerebral thrombosis and brain abscess. Low pressures are seen in fainting and shock. The pressure is often low in headache after lumbar puncture also in long-standing degenerative diseases of the nervous system. Valuable diagnostic information may be had by studying the pressure from two sources at once and by studying the change in pressure with the withdrawal of fluid. Ayala's index is given and may be useful in diagnosis.

Comparison of Gold Chlorid, Benzoin and Mastic Tests on Cerebrospinal Fluid.—COCKRILL (*Arch. Neurol. and Psychiat.* 1925, 14, 455) studied 400 routine spinal fluids from 334 patients by the three methods. The cases comprised neurosyphilis, syphilis without nervous system involvement, nonsyphilitic and various pathologic conditions, as meningitis, multiple sclerosis and general medical cases, including many nonsyphilitic neurologic conditions. In 384 instances the three tests gave similar reactions; in 16, dissimilar. The author feels that the benzoin test is simpler for routine examination but in certain diseases, as meningitis and multiple sclerosis, the colloidal-gold test is preferable. A table of data summarizing the study is given.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Proliferative Reaction to Stimuli by the Lytic Principle.—The arguments in favor of a reaction of proliferation in the presence of the lytic agents are put forth by HADLEY (*J. Infect. Dis.*, 1925, 37, 35), giving further support to the observations made by d'Herelle and Bordet and Cuica. The latter workers, however, used liquid media, which seems a less precise method of estimating the growth than agar, as employed by the author. Bacillus pyocyaneus was the organism studied, and it was found that the lytic agent being present, two types of colonies grew, the more rapidly growing, the L. colonies, were subject to the appearance of irregularities and clearing areas, evidencing lysis, while the other type, the R. colonies, seemed insusceptible to this action. The lysed colonies demonstrated "transmissible lysis," while the R. colonies showed the presence of no such agent on transfer. Although the evidence of the lytic phenomenon in the Bacillus pyocyaneus cultures differs widely from that pictured by d'Herelle working on the Shiga bacillus, nevertheless the author urges that it is but

another manifestation of bacteriophage. The interrelationship between organism and lytic principle seems in the nature of host and parasite, to which the host organisms develop a varying degree of resistance, which is of three orders: (1) Those absolutely susceptible to lysis; (2) those with a moderate degree of susceptibility to the lytic agent; (3) a resistant type, as illustrated by the R. colonies. It would appear that the function of the lytic agent is as much to stimulate the multiplication of the host, perhaps to insure its own future, as to carry on lytic action. This proliferative action is claimed by the author to be no evidence of the bacteriophage being an ultravirus, as upheld by d'Herelle for he points out that soot and creosote also stimulate the same proliferative response. In conclusion the article urges that the nature of the lytic agent be not finally considered as a living corpuscle but judgment should remain open to the possibility of its being either chemical or mechanical. Also this phenomenon is not to be confined to the colon-typhoid group, but should be regarded as varying in manifestation in several other groups of organisms.

Cholera Vibrion Statistically Studied as to Form and Growth.—To meet the assertions of those workers who claim that the pleomorphism shown by the cholera vibrion and other bacteria is an evidence of a complicated life history, HENRICI (*J. Infect. Dis.*, 1925, **37**, 75) has put forth carefully taken data to show that the variation in contour is to be correlated with the rate of growth. A five-day beef extract culture of the cholera vibrion, which showed the complete range of described forms, was used for transfer to uniform agar slants. These tubes were sampled at regular intervals up to ten days, and in each case the growth was analyzed as to enumeration, size and shape of the organisms, the results being obtained by special methods, devised by the author. All forms of the organism were noted during the period of sampling, viz: bacillary, vibrion, spherical and budding types. The bacillary form was found to be predominating up to thirty-six to forty-eight hours, at which time the numbers were at their height after which the more irregular forms showed a progressively greater frequency. The spherical form was found to be in the majority when the bacterial numbers were declining. The budding types stained with Congo-red, an indication of dissolution and not a reproductive stage. The conclusion followed that the pleomorphism so characteristic of this organism is to be ascribed entirely to the rate of growth; during the phase of positive acceleration the bacillary forms predominate, while during the phase of negative acceleration the vibrion, spherical and budding forms are in the ascendency.

Bacterial Factors in Pyorrhea Alveolaris.—In an attempt to discover the causative agent in pyorrhea alveolaris a great many studies on the bacterial flora of the mouth have been undertaken. Miller (1890) found butyric acid without discovering the causative organism; Rodella (1905) isolated Bacillus putrificus, which was confirmed by Kligler, but sugar fermentations of these show this to be an inclusive group; in 1917 Hall obtained Bacillus bifermentans in association with streptococcus, and many more isolations have been reported. The experiments reported by HALL (*J. Infect. Dis.*, 1925, **37**, 88) were undertaken

to determine if sporulating anërobes were to be found in the mouth. Saliva was taken from 43 persons after breakfast, before brushing the teeth, and 1 cc. inoculated into brain medium, which was heated to 80° C. for twenty to thirty minutes, to destroy all but the spores. In only 6 cases were anërobes found, four distinct organisms: Bacillus welchii, 3; Bacillus bifermentans, 1; Bacillus tetanomorphus, 1; Bacillustetani, 1. In 3 of these cases caries was present. None of these anërobes were found to appear in successive cultures and no definite association of them with pyorrhea could be ascertained with the possible exception that some anërobes may cause irritating calculus depositions from the saliva.

Yeasts from Human Sources.—In view of the interest evoked by the yeasts of sprue and thrush, the work of PECKHAM (*J. Infect. Dis.*, 1925, **37**, 53) is significant in pointing out that of 51 yeasts obtained from human sources (mouth, throat, bronchi and vagina) 41 were pathogenic, the majority of these coming from the oral region. These yeasts were tested by inoculation into the groin and peritoneum of guinea pigs, producing local and disseminate abscesses, throughout the internal organs. One yeast was taken for intravenous inoculation of two rabbits and a blood-picture change resulted, of prompt lymphopenia, a secondary anemia and endothelial-cell proliferation. The immunized rabbits showed antibody formation but no glycosuria nor albuminuria. The immunized guinea pigs, on metabolic studies, showed a diabetic condition, while the postmortem finding in the more chronic infected cases was an extensive fibrosis of the islands of Langerhans. The author suggested that this may indicate a possible means of producing diabetic animals. THOMAS (*J. Infect. Dis.*, 1924, **35**, 407) showed the frequency of infections in guinea-pigs by organisms of the enteritidis-paratyphoid B group after exposure of the animals to cold, injection of other bacteria and in untreated animals, and also that striking changes were to be found in the islands of Langerhans in these animals. Menten demonstrated that these hydropic degenerative changes are correlated with variations in blood sugar. Such findings must be considered in interpreting results of experimental injections particularly in guinea pigs.

The Typhoid-Paratyphoid Group in Water Supplies.—As a result of the discovery of Bacillus paratyphoid B in various material during an investigation of an epidemic at Steinau, KAPELLER (*Centralbl. f. Bakteriol.*, 1925, **96**, 8) showed that with comparatively small amounts from the city water supply the presence of a Bacillus paratyphosus B was readily demonstrated. At the time of the examination of the water the epidemic was over and no cases of the disease existed. Therefore the literature was covered to find instances of water contamination with the typhosus-paratyphosus group. Kacyznski (1912) found eight typhoid bacilli in a liter of the Lemberg water supply, and therefore urged a more careful investigation, from a bacteriologic standpoint, of all water supplies. The incidence of contamination with this group of organisms is shown by the findings of 34 workers, widely scattered throughout the world, of 37 infected water supplies, as reported up to 1922. Of this number 33 contained typhoid bacilli, 4 Bacillus

paratyphosus B and 2 Bacillus paratyphosus A. Two of the Bacillus typhosus were in combination with Bacillus paratyphosus B. The finding of these bacteria was usually in isolated samples, and could not be demonstrated on daily examinations. This, together with the relatively long incubation periods of the considered diseases, added to the difficulty of correlating results. This accidentally discovered contamination with typhosus-paratyphosus group of bacteria without the association of an epidemic, and the comparative frequency of finding this group of bacteria as reported in the literature points to the necessity of a closer laboratory vigilance of water supplies.

Mechanical Irritation as Etiologic Factor of Cancer.—ALTER (*Am. J. Pathol.*, 1925, 1, 511) reported a case which appears to present a striking example of mechanical irritation as an etiologic factor in the histogenesis of cancer. This case was that of a man, aged sixty years, who for one year previously had increasing constipation, loss of weight and finally obstruction. Operation revealed a new growth in the sigmoid. This growth was an annular type of carcinoma. Fitting into the lumen of the constricted portion with a ball valve-like action was the head of a long pedunculated polyp. The stalk of this was 8 cm. in length. Above the constricted ring was a saccular dilatation of the bowel, and in this was lodged a peach stone. This part of the gut was much thickened. Both polyp and cancer showed signs of chronic inflammation. The bowel was resected, and the man is alive and well five years afterward. The suggestion is made that the polyp arose as a sequel to an inflammatory process. Hypertrophy of the bowel followed its continuous attempts to get rid of the polyp. The irritation caused by the head of this pedunculated growth hitting against the wall started the cancerous growth. Lodgment of the peach stone above the growth and the extra efforts to get rid of it caused the sac-like dilatation of the gut.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Irradiated Foods and Irradiated Organic Compounds.—STEENBOCK and DANIELS (*Jour. Am. Med. Assn.*, 1925, 84, 1093) state that by exposing such food materials as wheat, rolled oats, corn, hominy cream of wheat, shredded wheat biscuits, corn flakes, patent wheat, flour, cornstarch, meat, milk and egg yolk to ultraviolet light they can be endowed with rickets preventing properties. That such a wide

variety of foods can be thus affected appears to be due to the fact that practically all naturally occurring foods contain lipoidal constituents of the nature of sterols which can carry this activation. Cholesterol, for example, as obtained from brain is entirely inactive, but after exposure to ultraviolet light becomes rickets preventing. As fats are good solvents for these lipoids, practically all fresh fats, such as butter fat, olive oil, lard, corn oil, cocoanut oil and cottonseed oil, can be activated, often to a degree to make them compare favorably with cod liver oil. As antirachitic action consists in the induction of calcium assimilation and its conservation for the animals, this is a matter which concerns not only the young but also the adult. It is suggested that these findings may have their significance not only in nutrition, but also in the therapy of those diseases known to respond to irradiation with ultraviolet light.

The Cultivation of Endameba Histolytica.—Boeck and Drbohlav (*Am. Jour. Hyg.*, 1925, 5, 371) obtained in culture from two cases of amebiasis two strains of endemeba. These were morphologically identical with the endameba in the feces of the patients and with Endameba histolytica. The "K" strain was grown in cultures for eight months and eleven days and the "E" strain for three months. The most suitable artificial environment for the growth of Endameba histolytica was in either the L. E. S. (Locke egg serum) or L. E. A. (Locke egg albumen) medium, at a temperature of 37° C. An initial reaction of the medium of pH 7.2 to pH 7.8 is necessary. The cultivation experiments demonstrated that Endameba histolytica may eat bacteria in the absence of a preferred diet of tissue juices, extracts and red blood cells. Both strains isolated in cultures proved to be pathogenic for kittens in which they produced acute dysentery, colitis and in two kittens a liver abscess. The virulence of the amebæ was not influenced by prolonged cultivation. These experiments confirm the work reported by Cutler (1918) with respect to the cultivability of Endameba histolytica. The authors, however, were unable to produce encystment under the conditions through which he claims to have brought it about. Their own media proved to be more suitable for the multiplication of Endameba histolytica than the blood bouillon medium. Encystment occurred in a culture of the "E" strain of Endameba histolytica on only one occasion. The L. E. S. and L. E. A. media have proved suitable for the cultivation of Endameba histolytica, Chilomastix mesnili, Trichomonas confusa, Chilomastix gallinarum, Trichomonas gallinarum, and has maintained Endameba coli and Endolimax nana for a period of three days.

The Relationship of Hard Water to Health: I. Hard Water as a Possible Factor in Urinary Concretion Formation.—Myers (*J. Infect. Dis.*, 1925, 36, 576) states that oxamid fed to rabbits produced only a slightly larger amount of solid material in the urinary bladder when the rabbits received hard water than when they were given distilled water. Glass beads placed in the kidneys of dogs produced concretions with both a hard and a distilled water intake. Glass beads in the kidneys of albino rats failed to produce concretions with either type of water. No definite relationship was observed between hardness of the water intake and the amount of calcification of cartilage

blocks in the bladders of rabbits in conjunction with either a high- or a low-calcium diet. No evidence has been found proving hard water to be an etiologic factor in urinary concretion formation.

Complexity of the Scarlet-fever Toxin and Antitoxin.—PARK and SPIEGEL (*J. Immunol.*, 1925, 10, 829) state that the fact that an individual convalescent scarlet-fever serum neutralizes the toxin of a certain scarlet-fever streptococcus in certain susceptible persons and not in others proves that the toxic filtrate has more than one toxin and that a person may be susceptible to one component and not to another or others. We can conceive that the usual scarlet-fever strain makes a toxic filtrate containing the different toxins A, B, C and D. A less common strain A, C, D, E or B, C, D, E. Strains from some septic sore throats, C, D, H, I, and from some erysipelas cases, C, D, K, L. Antitoxins to a greater or less degree would develop in any person or animal injected with any toxic filtrate to neutralize the actual toxins present in the filtrate. The finding that a certain convalescent serum or antitoxin horse serum will fail to neutralize a toxin for certain persons in the same quantity which is successful in others, but in larger amount succeeds, proves that the antitoxic response is different for the different component toxins either because of the different proportions of the toxins in the filtrate or because the child or animal responds differently in degree to the stimulus of the different toxins. We have the analogy of horses receiving the same amount of diphtheria and tetanus toxin. Some produce strong antitoxin for diphtheria but weak for tetanus and others strong antitoxin for tetanus but weak antitoxin for diphtheria. A convalescent scarlet-fever serum from a single patient may fail to cause blanching in a true case of scarlet fever because the two cases are due to two strains that differ in at least one toxin and so in one induced antitoxin. It is also probable that there are strains of streptococci that have the power to produce scarlet rash, producing toxins which are quite different from the standard Dick strains, so that after convalescing from infection due to one strain a second infection might occur from the other strain. Every year a few cases sent into the hospital with the diagnosis of scarlet fever after recovery develop a second attack. We have been inclined to think that the first attack was not scarlet fever, while if we had made a culture, possibly a strain of streptococci that made different toxins from the usual cases would have been found. If this assumption is true a case of scarlet fever at onset might give a negative Dick test to the Dick strain toxin, and its serum would then neutralize the standard toxin and blanch the rash of an ordinary case of scarlet-fever. The point is that it is not safe at the present time to limit the diagnosis of scarlet fever to cases due to the usual strains making the standard group of toxins. At most, the exceptional strains cause only a small minority of the cases of scarlet fever. Cases that do not respond to the serum should be studied carefully to determine whether their strains are typical ones. It is possible that in these a polyvalent antitoxic serum is indicated, or it may simply be that the scarlet fever streptococci or other streptococci or other microörganisms have invaded the deeper tissues and are beyond the help of antitoxins. Further investigation is necessary to determine the value of a bactericidal serum in these cases.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF NOVEMBER 16, 1925

The Fate of Ingested Benzoic Acid in the Dog.—ARMAND J. QUICK (from the Department of Physiological Chemistry, University of Pennsylvania). Since most of the studies of benzoic acid conjugation have been carried out on animals which excrete benzoic acid quantitatively as hippuric acid, little attention has been paid to other conjugation products of benzoic acid. Past studies on the dog, however, have indicated that the production of hippuric acid is comparatively small and that the urine, following benzoic acid administration, contains glycuronic acid. Owing to inadequacy of the analytic methods available, no quantitative studies of the relationship of hippuric acid, benzoyl-glycuronic acid and free benzoic acid have been made. Analytic procedures were devised for the direct determination of hippuric acid and of benzoyl-glycuronic acid, and these methods were then employed in the study of the conjugation of benzoic acid in the dog. It was found that ingested benzoic acid was completely conjugated and excreted partly as hippuric acid and partly as benzoyl-glycuronic acid. The quantity of hippuric acid, however, was comparatively small and relatively fixed in amount, while the benzoyl-glycuronic acid was variable, depending upon the quantity of benzoic acid in excess of the organism's capacity of synthesizing hippuric acid. Exogenous glycine, either free or combined, caused a definite but small increase in the production of hippuric acid. These findings emphasize the importance of the glycuronic acid conjugation of benzoic acid, and the limitations of the hippuric acid synthesis in dogs even when the organism is offered large quantities of exogenous glycine.

The Growth of the Nervous System and the Behavior Pattern.—G. E. COGHILL (from the Department of Anatomy of the University of Kansas). The work upon which this report is offered has been made upon embryos of amblystoma. It represents an effort to analyze the nervous system upon the basis of behavior and to explain behavior upon the basis of nervous structure. It is hoped that the following conclusions may be of interest to physiologists: (1) The behavior pattern of amblystoma develops according to a regular order of sequence of movements. The muscles of the embryo are a longitudinal series of segments (myotomes). The first movement is a contraction of the anterior muscles (flexure). Progressively in time the contraction extends farther through the series of muscles until finally the entire series on one side only contracts and causes the animal to assume a tightly coiled condition (coil reaction). This signifies the attainment of full power of contractility by the muscles. Any particular movement begins in the anterior region and progresses tailward, according

to the order of its embryologic development. During the coil stage the movements are almost universally away from the side stimulated (avoiding reaction). Up to the coil stage there has been simply a gradual development of the flexure to its extreme limit, the coil. There then appears instantaneously a new pattern in the reaction: a flexure, beginning at the anterior end and progressing caudad, is followed by a second flexure in the opposite direction before the first has reached the caudal end of the system. Such movements in series, each pressing backward upon the water, produce locomotion (the swimming reaction). (2) This behavior has a definite and specific counterpart in nervous organization, and the order of development in structure explains the order of development of the behavior. The motor axones are collateral branches from descending tract axones. Stimuli can enter this tract only in its anterior part because afferent neurones undergo synapse, not with motor neurones of the same side, but with commissural neurones which exist only in the anterior region. This arrangement insures crossed reflexes and anterioposterior (cephalocaudal) progression of muscular contraction. The first reactions are made possible by the growth of the commissural cells between an already existing sensory tract of one side with an already excisting motor tract on the other. The instantaneous appearance of the swimming reaction in perfect form is explained by the growth of collaterals from the axones of anteriorly located tract neurones into synapse with the commissural cells so that an excitation that is passing directly to the muscles of one side is shunted off to the muscles of the other, but delayed in passage by the intercalation of at least one additional neurone in the course. (3) The functioning neurone is a growing structure, and its growth extends its own function and that of the nervous system as a whole. This is shown not only by the instances cited above but particularly by the motor root fibers. Many of the motor roots, after the muscles (myotomes) have acquired full function in locomotion, consist of only one fiber. This fiber branches with sufficient profusion over the muscle to innervate all of its cells, while the terminal branch of the fiber is growing entirely beyond the muscle into the primordium of the limb, and at a time long before limb muscle is differentiated. The growth of functional neurones into nonfunctional primordia opens an important field of inquiry, bearing, as it does, upon problems of physiology, pathology and hygiene. (4) There is a pronounced periodicity in the development of sensitivity (investigations jointly with Dr. R. W. Watkins). This may be due to alternation of periods of growth with periods of function in the nervous system. Since embryos from the same batch of eggs conform in the main to the same rhythm, the periodicity would seem to have its inception at the time of fertilization of the egg. (5) The motor mechanism of amblystoma is probably the prototype of integrating mechanisms in mammals. The ventral horn neurones of man are longitudinally oriented (Lhermitte and Kraus) and collaterals go from their axones back into the gray. The motor cells that integrate arm flexion (analogous to trunk flexure in amblystoma) are distributed through five cord segments. Longitudinal conduction through this column of cells by means of the axone collaterals, the fasciculi proprii or the longer tracts may be the mode of integrating muscles for elementary components of the

The Kinetics of Osmotic Swelling in Arbacia Eggs.—MORTON MCCUTCHEON and BALDWIN LUCKE (from the Laboratory of Pathology, School of Medicine, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.). The volume of living cells is conditioned by a number of factors, an important one being the concentration of the surrounding medium with which the cell contents are in dynamic osmotic equilibrium. In order to study the rate of volume change resulting from osmotic changes, and the conditions that influence this rate, it is necessary to use *isolated* cells, the viability of which can readily be tested. An almost ideal cell for such an investigation is the unfertilized egg of the sea urchin. In the present study it is shown that the rate of swelling of these cells follows well-known diffusion laws, but that because of the presence of a semipermeable membrane enveloping the cells, other factors than diffusion come into play. The regularity with which the various processes pursue their course is such that events may be calculated; it is found that a good agreement exists between the observed and the calculated results. The rate of swelling of arbacia eggs in hypotonic sea water, over wide ranges of temperature and concentration, is found to follow the equation $\frac{dx}{dt} = k\,(a - x)$, when a is the difference in volume of the cell at the first instant and at equilibrium, x the volume change up to a time, t, and k the velocity constant. (See R. S. Lillie: *Am. J. Physiol.* 1916, 40, 249.) The rate of swelling, while primarily regulated by diffusion forces, is influenced also by other processes occurring in the semipermeable membrane. Evidence for this assertion is furnished by the effects of temperature and of concentration on the rate. Calculations made from the values of k at various temperatures show that the temperature coefficient is high, from 2 to 3, for a change in temperature of 10°, corresponding to a chemical rather than to a diffusion process. Calculated from the Arrhenius equation, the heat of activation ranges from 12,000 to 19,000 calories. The rate of swelling is greatly affected by the osmotic pressure of the sea water, and in a way not explainable on the grounds of a pure diffusion process. It requires very much longer for the cells to reach equilibrium in a mixture of 40 parts of sea water to 60 of distilled water than when 80 parts of sea water to 20 of distilled water are used. There is a corresponding change in the velocity constants. In a typical experiment at 15° C. the value of k in 20 per cent sea water was 0.006; in 40 per cent sea water, 0.012; in 60 per cent sea water, 0.024; in 80 per cent sea water, 0.072. On these grounds it is concluded that processes of unknown nature occur in the semipermeable membrane, and modify the effects of diffusion.

Studies on the Inorganic Composition of Blood.—S. E. KERR (from the Department of Physiological Chemistry, School of Medicine, University of Pennsylvania). After hemorrhage the blood volume is restored by the inflow of body fluids. The composition of the diluted blood will vary, however, depending upon the source of the diluting fluid. Water from the gastrointestinal tract will cause a diminished concentration of all the constituents. Lymph will cause a decrease in the potassium and possibly protein of serum. Intracellular fluid, such as that of muscle (the water and inorganic salts) is low in sodium and

chlorid and high in potassium and magnesium and, therefore, might cause a decrease in the sodium and chlorid and a rise in the potassium and magnesium concentrations of serum. A study was made with the hope of obtaining information concerning the main source of the fluid which restores the blood volume after hemorrhage. Determinations of specific gravity, water, sodium, potassium, chlorids and inorganic phosphates were made in serum and corpuscles; calcium, magnesium and protein in serum alone. Improvements were made in the methods for estimating sodium and potassium. A single hemorrhage, amounting to from one-third to one-half of the total blood volume resulted in a slight decrease in both sodium and chlorid of serum, and no significant change in corpuscles. Repeated severe hemorrhage produced a greater fall of sodium and chlorid of serum, a large increase in the potassium concentration of the corpuscles and an increase in the inorganic phosphate of serum. No changes in the potassium, calcium or magnesium of serum were observed. These observations, together with other indirect evidence obtained from the literature, indicate that a considerable part of the fluid entering the blood stream after hemorrhage comes from within the tissue cells. With hopes of obtaining an explanation of the unexpected rise of potassium in corpuscles after hemorrhage other experimental procedures were studied. The concentration of potassium of the serum was diminished by bleeding and infusing a solution of gelatin and sodium chlorid. The potassium concentration of the corpuscles rose more rapidly than with bleeding alone. Overdosage with insulin resulted in a fall of serum potassium and a rise of cell potassium. Subcutaneous injections of sodium oxalate caused a large increase in serum potassium with a corresponding increase in the corpuscles. It seems most probable that in all of these experiments potassium has permeated into the red cell, an observation contrary to the general teachings at present. The forces controlling the curiously unequal distribution of potassium between plasma and corpuscles are obscure.

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ORIGINAL ARTICLES.

STUDIES OF THE VASCULAR CHANGES IN CASES OF POLYCYTHEMIA VERA.

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The physiological factors which are disturbed in polycythemia vera are chiefly related to: (1) Augmentation of the volume of the circulating cells and the total volume of the circulating blood, and the consequent vascular accommodation; (2) increased viscosity of the blood; (3) organic disturbances in the bloodvessels; (4) secondary thrombotic processes; (5) pathological changes in the erythrogenetic tissue; (6) disturbances in metabolism, related to heat, water and mineral balances.

The factors concerned with the adjustment of the vascular system to increase in volume and variations of the volume in the different stages of the disease are of extreme interest. In this disease, the effects, which a persistently large volume of blood with a relatively greater increase in its cell content than in its plasma content has on the circulatory system, can be studied. In a previous report[1] the relationship between the size of the capillaries of the skin and the volume of the blood was discussed. It was shown that the capillaries and the venules of the skin have a storage function under stress, and that the capacity for this storage is provided by the distention and, as has since been demonstrated, the utilization of all the available capillaries of the skin. The accommodation of

the bloodvessels to the increase of blood volume in polycythemia vera apparently occurs first in the vascular internal organs, the spleen and the liver and in the large veins. With progression of the disease and greater increase of the blood volume, the peripheral veins, and eventually the venules and capillaries of the skin, take part in the accommodation. It was observed that in older patients capillary distention did not extend into the arterial segments of the capillaries, as it did in the younger persons. The distention of the capillaries and venules is frequently extreme, which explains in part the changes in the color of the skin and mucous membranes so characteristic of this disease. The capillaries can often be recognized macroscopically in the nail-fold as fine red streaks. There is retardation of the flow in the capillaries, with a tendency toward stasis and peripheral cyanosis from cold. The disease on this basis is an erythrosis with a marked tendency toward cyanosis.*

Studies have been made in a larger group of cases (14) during 1924, with relation to: (1) Correlation of vascular distention and the degree of increase in the volume of blood; (2) comparative studies of the color of the skin, the capillaries and the blood volume; (3) arterial, venous and capillary pressures; (4) renal function; and (5) basal metabolism.

Eight of the patients in this group were males and 6 were females. The average age was fifty-one years. The youngest was thirty-seven and the oldest sixty-three. There was no particular relationship to geographical distribution. Two of the patients came from mountainous districts, but the majority were from the middle west.

Hemoglobin and Erythrocytes. The erythrocyte count was increased in every case, and the range varied from 5,500,000 to 9,050,000 for each cubic millimeter, the average for the group being 6,890,000. The hemoglobin varied from 142 to 160 per cent by the acid-hematin method, and averaged 152 per cent. In grams of hemoglobin for each 100 cc. of blood the range varied from 16.8 to 23 and averaged 21.†

Viscosity. Estimations of the viscosity of the blood have been made as a routine in all cases by means of the Hess viscosimeter. The normal ratio of water to blood is 1 to 4.5. A ratio of 1 to 5 has been accepted as the upper limit of normal. A very marked increase in viscosity was present in all cases. A return to normal occurred only with the development of a subnormal red cell count

* Lundsgaard and Van Slyke found a normal oxygen saturation of the arterial blood in a case of polycythemia vera. We have verified this in 3 cases. They note that the patients become cyanosed very readily in this disease. This they explained on a twofold basis: (*a*) the increased hemoglobin content, which magnifies the influence on capillary unsaturation; (*b*) increased width, and number of skin capillaries. We would call attention to another factor, the retardation of capillary flow due to increased viscosity and capillary distention.

† The normal value is 13.8 gm. according to the Haldane standard; 15.6 (Haden); 16.8 (Williamson).

TABLE I.—BLOOD VALUES IN POLYCYTHEMIA VERA.

Case.	Age, Sex.	Date.	Treatment remarks.	Height, cm.	Weight, kg.	Surface area, sq.m.	Plasma.			Hematocrit.		Total blood.			Erythrocytes.		Hemoglobin.	Viscosity (normal 1:4.5).
							Volume, cc.	Cc. for each mg.	Cc. for each meter of surface area.	Erythrocytes, per cent.	Plasma, per cent.	Volume, cc.	Cc. for each mg.	Cc. for each sq.m.	No. per cu.mm. millions.	Per cent.	Gm. for each 100 cc. blood.	
1	56	6-30-24	.....	185	70	1.92	4340	61	2260	70	30	14,650	209	7640	6.05	166	22.9	1: 9.8
	M.	8-16-24	Bleeding and roentgen-ray	...	70	....	4440	63	2310	40	60	7,400	105	3860	....	...	....	1: 5.8
2	61	.....	.....	164	53	1.57	3430	64	2180	58	42	8,170	154	5200	6.63	152	20.9	1: 8.5
	F.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	8.31			
3	47	.....	.....	170	62	1.72	3950	64	2300	65	35	11,300	182	6570	8.93	145	20.0	1:11.2
	M.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	8.90			
4	51	4-28-24	.....	174	63	1.76	4800	76	2730	60	40	12,000	190	6820	6.40	145	20.0	1:10
	M.	6-10-24	Bleeding and roentgen-ray	...	..	....	4500	71	2560	51	49	9,200	146	5220	6.11	121	16.8	1: 6.2
5	37	4-14-24	.....	172	50	1.58	4500	90	2850	57	43	10,460	209	6620	6.22	142	20.0	1: 9.6
	F.	5-20-24	Bleeding and roentgen-ray	...	50	....	3600	72	2280	50	50	7,200	144	4550	5.84	130	18.0	1: 7.1
6	42	.....	.....	164	60	1.65	2710	45	1640	62	38	7,100	126	4300	6.67	154	21.0	1:10
	F.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	6.41			
7	63	7-11-24	.....	174	73	1.88	3430	47	1820	60	40	8,570	117	4560	5.50	145	20.4	1: 7.4
	M.	7-31-24	.....	...	74	1.89	4140	55	2190	59	41	10,100	136	5350	6.90	142	19.8	1: 5.8
		8-20-24	.....	...	73	1.90	3560	48	1870	47	53	6,720	89	3530	....	145	20.3	
8	44	.....	.....	190	59	1.82	3710	63	2040	62	38	9,760	165	5360	7.41	160	24.0	1:10.2
	F.																	
9	42	.....	.....	182	81	2.1	3750	46	1780	67	33	11,350	140	5400	7.55	170	23.0	1:12
	M.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	8.58			
10	52	.....	.....	159	50	1.5	3330	66	2220	56	44	7,570	150	5040	5.57	141	20.0	1: 7.6
	F.																	
11	59	12-29-23	Bleeding and	185	68	1.9	4340	63	2270	60	40	10,840	160	5700	7.15	155	21.0	1: 9.4
	M.	1- 7-24	roentgen-ray	...	68	1.9	4500	66	2370	55	45	10,000	147	5280				
		6-17-24	.....	...	..	....	5000	73	2630	30	70	7,140	105	3750	....	83	11.5	1: 3.7
12	55	.....	.....	153	54	1.5	2860	52	1900	59	41	9,200	170	6140	9.11	142	20.4	1: 9.8
	F.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	9.05			
13	50	.....	.....	185	70	1.92	4240	60	2200	65	35	12,100	172	6300	5.50	155	21.3	
	M.	.....	.....	...	..	....	....	..	....	..	..	.....	...	....	6.60			
14	62	12-15-24	.....	177	60	1.75	3640	60	2070	67	33	11,000	183	6280	7.85	165	22.5	1:13.2
	M.																	
		Average	values				3800	60	2160	62	38	10,300	166	5850	6.89	152	21.0	1:9.9

TABLE II. DATA RELATIVE TO VASCULAR SYSTEM IN POLYCYTHEMIA VERA.

Case.	Age, Sex.	Blood-pressure.		Peripheral veins.	Peripheral arteries.	Retinal vessels.	Heart.	Electrocardiographic findings.	Splenic enlargement.	Hepatic enlargement.	Data relating to size of capillaries of the skin.	Symptoms referable to vascular system.
		Systolic.	Diastolic.									
1	56 M.	155 170	110 90	....	....	Veins full and dark, exaggeration of arterial *reflex*, arteriovenous compression	Enlarged 2	Diphasic T in Lead I	3	2	Long loops with distention 2 of venous limbs, relative contraction of arterial limb; 33 per cent. of loops tortuous	Dyspnea and substernal distress on exertion. Mental apathy. Increasing redness of skin.
2	61 F.	124	82	Not abnormal	.....	Veins full and dark	Not enlarged	....	Hard 2	2	Short loops. Distention 3 of venous limbs. Relative contraction arterial limb; 90 per cent tortuous loops	Hematuria, hematemesis, vertigo.
3	47 M.	145	95	....	Feeble pulsation in vessels of right leg	Negative	Not enlarged	....	3	0	Short loops. Venous engorgement 2	Claudication in right leg sign of arterial blocking. Painful attacks of cyanosis in second and third fingers of right hand.
4	51 M.	130	95	Hemorrhoids 1	.....	Retinal veins full and dark. Contraction of arteries	Not enlarged	....	2	2	Dilatation 2 of venous loops. Moderate contraction of arterial loops; 15 per cent tortuous loops. Many open capillaries	Fatigue and weight loss, only symptoms.
5	38 F.	125	85	Varicose veins both legs	.....	Veins large and dark	Not enlarged	....	3	1	Venous enlarged 1; 25 per cent of loops tortuous	Moderate vertigo, fatigue, loss of weight 10 pounds. Increased color in face.

6	42 F.	120	80	Hemorrhoids	.....	Negative	Not enlarged	Negative	2	1	Arterial and venous limbs engorged 2; 10 per cent of loops tortuous	Heightened color to skin for two years no dyspnea, vertigo 1+.
7	63 M.	140	106	.....	.....	Veins full, dark, contraction of arteries	Not enlarged	Negative	2	0	Engorgement 3 venous limbs contraction 2 of arterial limb	No dyspnea or vertigo.
8	44 M.	128	68	.....	.....	.....	Negative	....	1	2	Distention 3 venous limbs, 2 arterial limbs, few hemorrhages	No dyspnea, vertigo or edema, gastric symptoms marked.
9	47 M.	135	98	Varicose veins	Throbbing carotids	Veins full, dark, tortuous	Negative	....	2	0	Distention 3 venous limbs. Contraction 1 arterial limb	Vertigo, weakness, intolerance to extreme heat or cold, deafness.
10	52 F.	122	64	.....	.....	Negative	Negative	Negative	2	0	Venous limbs engorged 3. Contraction 1 arterial limb	Melena, hematemesis. Exhaustion and headaches.
11	59 M.	182	106	.....	Calcified arteries of leg	Mild retinal arteriosclerosis	Pulse 120	Negative	1	0	Contraction 2 of long arteriosclerotic loops	Weakness, headaches. One cerebral seizure without paralysis.
12	55 F.	170	90	.....	Peripheral arteries sclerosed 2	.....	Enlarged 1, systolic mitral and aortic blow 0	....	2	0	Long capillaries, engorgement 3 of arterial and venous limbs	Dyspnea 2 on exertion, epigastric pains with fear of impending death.
13	50 M.	114	90	Dilatation smaller venules, hands and face	Calcified arteries leg	Veins full and dark	Negative	Negative	2 not hard	3	Marked distention of venous limbs, relative contraction of arterial limbs	Dyspnea 1, attacks left upper abdominal pain, infarct, (?) splenitis.(?)
14	62 M.	130	85	Marked dilatation, smaller venules	No evidence of arteriosclerosis	Veins full and dark, some arteriovenous compression	Negative	Negative	1	1	Marked distention, venous and arterial limbs	Dizziness, polyuria attacks, tachycardia, loss of weight; excessive appetite.

and normal percentage of cells by the hematocrit. Even with a normal red cell count the viscosity was frequently increased; it is, therefore, a very important diagnostic finding (Table I). The viscosity bears a closer relation to the percentage of cells by the hematocrit and the hemoglobin than it does to the erythrocyte count.

Blood Volume. The total volume of the circulating blood as determined by the dye method was increased in every case. The average value for the group was 10,300 cc., or 166 cc. for each kilogram, or 5850 cc. for each square meter of surface area.

The volume of the circulating plasma showed a range of from 46 to 90 cc. for each kilogram of body weight. The average amount was 60 cc. for each kilogram, or 2160 cc. for each square meter of surface area.

Hematocrit Readings. The percentage of erythrocytes as determined by the hematocrit‡ varied from 58 to 70 per cent, the average being 62 per cent.

The Arteries and Veins. In Table II correlative data with respect to the spleen, liver, peripheral veins, capillaries and arteries are given. The condition of the retinal vessels, the size of the heart, the relative size of the spleen and liver, and the condition of the capillaries of the skin are noted in each case.

At the time of admission the complaints were mainly those relating to the vascular system. In 2 cases (Cases IV and VI) hemorrhoids were the chief complaint; in 2 (Cases V and IX), varicose veins of the legs; in 5, symptoms relative to disturbances of the peripheral arteries, symptoms in 3 being those of claudication, and in 2 diminished pulsation in the vessels of the leg was found. Roentgenological examination showed calcification of the arteries [illegible] Cases XI and XIII.

Ophthalmoscopic examinations were made in 13 cases, and of these the characteristic retinal picture was observed in 9 (64 per cent). In 3 cases the ophthalmoscopic report was negative. The positive findings were fulness and dark color of the veins with or without tortuosity. In 5 cases venous distention and arterial contraction, exaggerated arterial reflex and arteriovenous compression were observed. In 1 case observations were made on the retinal vessels and skin capillaries during the course of treatment with phenylhydrazin hydrochlorid. Engorgement of these vessels had entirely disappeared when the total blood volume was reduced to approximately 105 cc. for each kilogram of body weight.

The Heart. The size of the heart was noted in every instance. Enlargement 1 or 2 was present in 3 instances (Cases I, III and XII).

‡ A weighed amount of 10 per cent sodium oxalate solution was evaporated uniformly on the inside of hematocrit tubes, thus assuring a uniform distribution. One cubic centimeter of 2 per cent oxalate in solution was employed as a control and there was an average variation of 1 per cent.

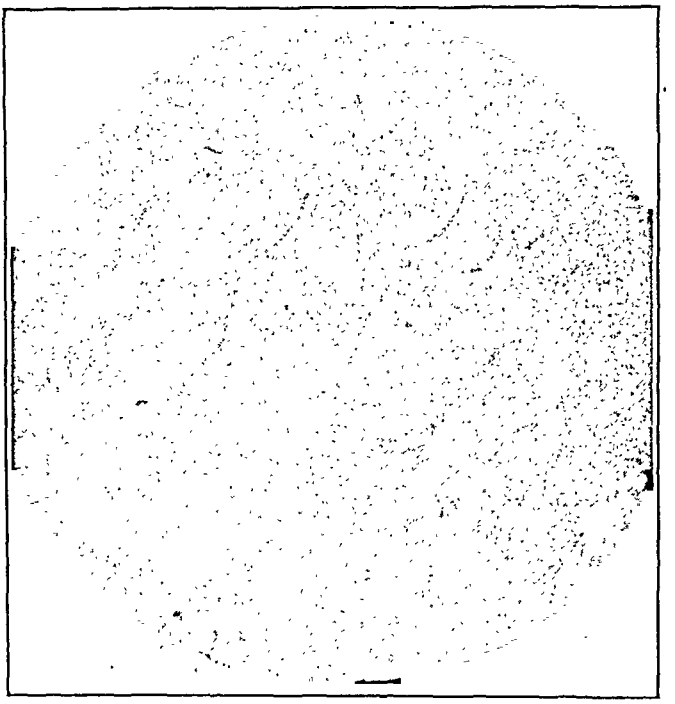


FIG. 1.—Photomicrograph of skin capillaries on back of hand in case of polycythemia. Note the large number of distended capillaries and venules in field. Only the tips of the loops are visible. × 25.

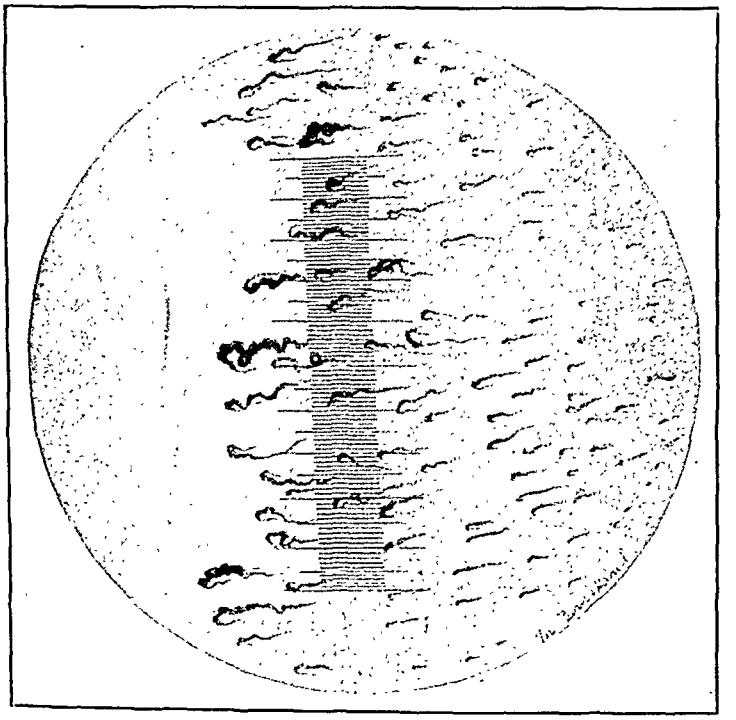


FIG. 2.—Polycythemia vera. Nail-fold capillaries. Sketch drawn to scale. Smallest division 0.01 mm. Note the distention of venous segment of capillary loop. Many loops in field. Blood volume 160 cc. for each kilogram of body weight.

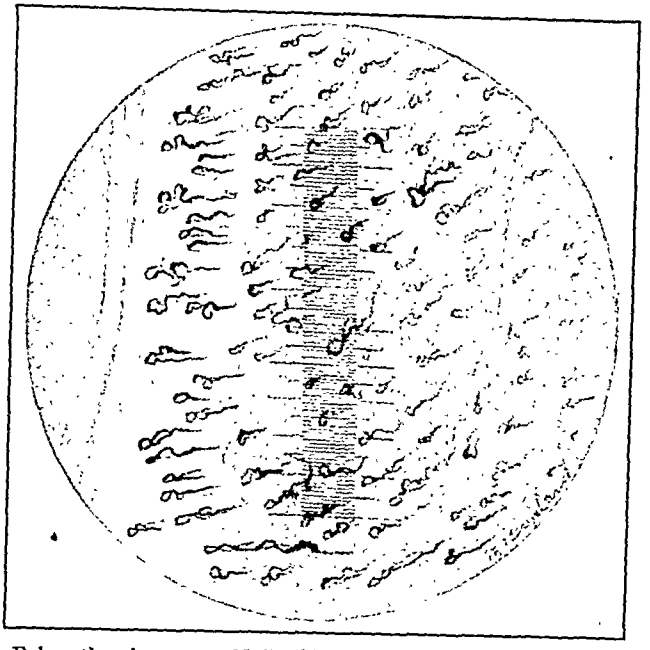


FIG. 3.—Polycythemia vera. Nail-fold capillaries drawn to scale. Loops less distended. Blood volume 137 cc. for each kilogram of body weight. Same case as in Figure 2.

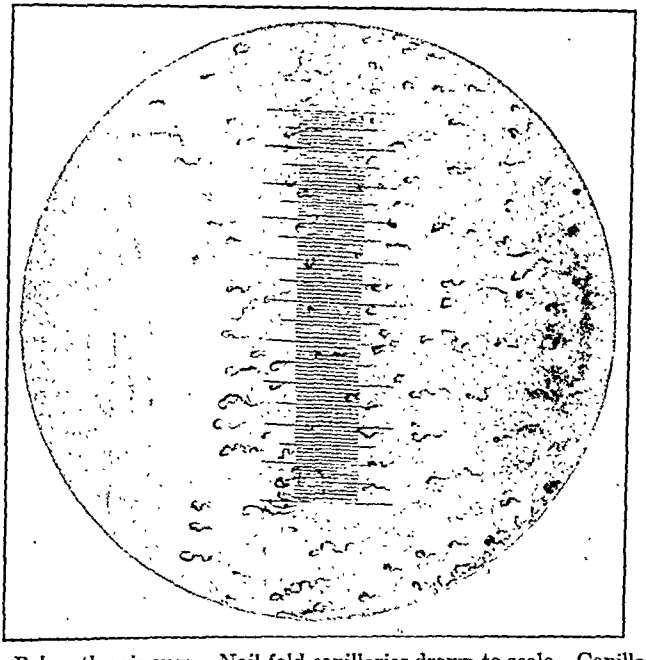


FIG. 4.—Polycythemia vera. Nail-fold capillaries drawn to scale. Capillary loops thin and difficult to see. There is a definite decrease in the number of open capillaries. Blood volume 99 cc. for each kilogram of body weight. Same case as in Figures 2 and 3.

There was no other evidence of cardiac disease except in Case XII, in which systolic mitral and systolic aortic murmurs were present. Electrocardiographic examinations were made in 6 instances, and no significant changes were present.

The Spleen. The spleen was enlarged in all the cases. In 3 the enlargement was graded 1; in 8, 2; in 3, 3. The spleen was usually firm and hard.

The Liver. The liver was enlarged in 8 cases, being graded from 1 to 3; in 6 the liver edge was not palpable.

The Capillaries. The capillaries of the nail-fold were examined in every case. Engorgements of the venous limb and collecting venules were graded 2 or 3 in 12 cases. Engorgement 1 or 2 of the arterial limb was noted in 4 cases. In 9 cases the arterial segment showed relative contraction. In Case VIII small capillary hemorrhages were seen. The percentage of tortuous capillaries, from 10 to 90, showed more relationship to age than to the degree of increase in the volume of the blood. A quantitative study of the number of open capillaries for each square millimeter of skin area was made in 2 cases; in Case XIV there was an average of 65 open capillaries for each square millimeter of skin on the back of the hand (Fig. 1). The average number in healthy persons varies from 15 to 40. The capillaries were studied in several cases during the course of treatment while a decrease in the total volume of the circulating blood was taking place (Figs. 2, 3 and 4). A progressive diminution in engorgement and number of open capillaries followed *pâri passu* the changes of volume.

Color Analysis of the Skin. Color measurement of the back of the hand, tongue or lower lip and cheek were carried out as a routine in 4 cases. The skin tintometer, as devised by Rowntree and Brown,[5] was used for direct color matchings. The tintometer values were originally standardized according to the Munsell system for color measurement.*

Direct color studies were made by the Munsell wheel and color disks for direct skin matchings. This is fairly satisfactory but is time consuming. There is some difficulty in matching flat colors to the live skin color, but fairly accurate comparisons were made. Checked readings by different observers have shown a range of error up to 20 per cent, which is low as compared with ordinary clinical methods. Color analyses have been made in other cases and are now being made as a routine.

* The Munsell system of color measurement employs a series of color disks with perforations and slits allowing the disks to be superimposed, exposing various segments of each. The disks are then spun on a motor shaft, thus optically mixing the colors. Color according to this system is measured according to hue, value and chroma. The color measurements according to hue, value and chroma are printed on the back of each disk. Five primary and five intermediate hues are utilized. Hue is indicated by the color abbreviation as R = red, RP = red purple; value by the numerator, and chroma by the denominator of the fraction.

COLOR ANALYSES IN CASE V.

Area	Color readings.		Blood volume.	
Cheek	R 4/8	0.48	209 cc. for each kilogram.	
	P 3/3	0.38		
	YR 8/5	0.14		
			Color analysis in a normal blonde.	
Knuckle of right hand	R 4/8	0.37	R 7/5	0.33
	P 3/3	0.33	B 7/2	0.42
	YR 8/5	0.30	YR 8/5	0.25

Blood Pressure. The average arterial blood pressure in the 14 cases was 138 systolic and 90 diastolic. In Case I, XI and XII there was a mild hypertension with normal diastolic pressure and a moderately high pulse pressure.

The venous pressure was determined by the Hooker method in Case XIV, on the peripheral veins of the back of the hand at heart level. The average of six determinations was 15 mm. of water. This reading is slightly higher than normal.

The capillary pressures were determined in 1 case by the Danzer-Hooker method on the capillaries of the nail-fold. The values are expressed in millimeters of mercury and are approximately normal according to this method: Small capillary: 14, 12, 14; large capillary: 15, 17, 18.

TABLE III.—RENAL FUNCTION STUDIES IN POLYCYTHEMIA VERA.

Case.	Blood-pressure.		Urine.			Blood.		Phenolsulphonephthalein excretion in two hours, intravenously, per cent.
	Systolic.	Diastolic.	Albumin.	Casts.	Erythrocytes.	Urea mg., for each 100 cc.	Uric acid, mg. for each 100 cc.	
2	124	82	2	Hyaline and granular	0	..	....	45
4	130	95	3	Few leukocytes	1	30	....	30
7	140	106	0	Hyaline 1	0	..	....	45
8	128	68	1	0	0	47	4.9	40
9	135	98	3	Hyaline 1	0	..	....	50
11	182	106	2	Hyaline 1	0	28	3.8	
13	114	90	2	0	..	..	6.35	30
14	130	85	1	Granular 1	*	16	2.9	40

* Occasional.

Renal Function (Table III). The renal function was studied in 8 cases. Albumin, graded from 1 to 3, was present in all. Hyaline and granular casts were present in 6 cases. Erythrocytes were found in 1. The study of the chemistry of the blood showed slightly elevated blood urea in Case VIII. In Case XIII, a patient in whom there were clinical manifestations of gout, the blood uric acid was 6.35 mg. for each 100 cc. of blood. The excretion of

phenolsulphonephthalein in two hours was slightly decreased in 4 cases and moderately decreased in 2 (Cases IV and XIII). In the latter case signs of mild renal impairment were shown by the restricted range of specific gravity and by a definite lag in excretion of water according to the standard water test.

BASAL METABOLISM IN SEVEN CASES.

Case.	Rate.	Total blood volume, cc. for each kilogram.
5	+44	209
14	+37	183
13	+4	172
11	+9	160
9	+5	140
7	+22	136

The basal metabolic rate was increased in 3 cases and seemed to stand in some relationship to the higher levels of total volume of the blood.

Discussion. Most of the symptoms in polycythemia have a circulatory basis. From the standpoint of physiology the symptoms are of three types: (1) Those related to vascular distention and increased viscosity of the blood, as vertigo, sensation of fullness in the head, headache, hemorrhage and alterations in the color of the skin; this premise is borne out by the symptomatic improvement which follows a decrease in the volume of the blood and the number of cells; (2) those related to organic changes in the bloodvessels, either of an endarteritic or of a thrombotic nature, as infarction with localized pain (as splenitis); claudication and cerebral changes; and (3) those related to disturbances in metabolism, as loss of weight with excessive appetite, polydipsia, exhaustion and intolerance to heat and cold.

The symptoms due to distention are of the greatest interest because there is no other clinical condition so far as is known in which a persistent augmentation of the volume of the blood is present. The clinical symptoms produced by distention of the bloodvessels would, *a priori*, be most striking in relationship to the head. The headache in these cases is described as a generalized fullness and sensation of pressure and not as a throbbing pain. Vertigo is occasionally extreme, and at times change of position induces marked staggering. Hemorrhage occurs usually in the stomach or nose, less frequently in the brain, and rarely in the skin or kidney. Purpuric manifestations have not been observed. The relief from the cerebral symptoms afforded by bleeding, roentgenotherapy or by the use of phenylhydrazin hydrochlorid is striking. The symptomatic beneficial effects have been noted when there is a decrease approximating at least 25 per cent in the total volume of the blood. Complete relief is afforded when the volume is reduced to approximately 100 cc. for each kilogram of body weight. There is no direct

relationship between the severity of the symptoms and the degree of increase in the volume of the blood. The patients showing the largest volume of blood did not present symptoms of the distention type. Of the 6 patients with the largest volume of blood 4 presented symptoms of a general or metabolic type; 2 sought advice because of marked changes in the color of the skin, and 1 because of dizziness, polyuria and tachycardia.

There was apparently a relationship between the size of the spleen and the degree of increase in the volume of the blood. Three cases with the largest spleens (Cases I, III and V) also showed the largest volumes. The spleen was usually described as firm and rarely tender. In no case was there an extreme enlargement of the spleen similar to that observed in cases of leukemia. The liver was slightly enlarged, 2 and 3, in 7 cases. In only 1 instance was there an enlargement graded 3. No relationship existed between the degree of enlargement of the liver and the volume of the blood.

The appearance of the retinal veins is of interest and of diagnostic importance. The typical picture is that of distention of the retinal veins with or without tortuosity. They usually appear as full black streaks, and present a striking picture. Arteriosclerotic changes with contraction of the retinal arteries were present in 5 cases. The latter seemed to bear no relationship directly to the polycythemia, but more to the age and consequent degenerative changes in the vessels. Engorgement of the retinal veins was seen in 64 per cent of the cases, while typical engorgement of the venous portion of the skin capillaries was present in 92 per cent.

The response of the capillaries of the skin to the increase in the volume of the blood is twofold: Distention and enlargement of part or all of the capillary loop, and the opening up of all available capillaries. Krogh has shown in certain tissues that there is a relationship between the number of functioning capillaries and the metabolic requirement, and that at any given time under given conditions only a certain number of the capillaries are open. In polycythemia vera the capillaries and venules have an additional function, that of storage. The function of storage is effected not only by enlargement of these vessels, but by the use of all available capillaries. The reservoir function of capillaries and veins in experimentally increased volume of the blood has been shown by Meek and Eyster.[4] They found that 30 to 100 per cent of its volume may be added to the circulation without causing cardiac dilatation, while the capillaries and venules of the ear show dilatation and opening up of new channels.

In polycythemia vera, additional vascular space, is utilized with a loss or impairment of the physiological heat mechanism of the skin. The most important function of the skin is that of heat regulation. Cold produces a closure of many of the skin vessels with a decrease in the radiation of heat. When heat conservation

is unnecessary, and when heat dissipation is advisable, a large number of resting capillaries is available. In polycythemia this mechanism of heat regulation is impaired, since all available capillaries are continuously functioning. Many of the symptoms of polycythemia, such as intolerance to heat and cold, a burning sensation of the skin and the sense of suffocation, are made clear by this conception of the impairment of the mechanism of heat regulation. Engorgement and distention of the venous limb of the skin capillaries were found in all except 1 case, while enlargement of the arterial limb was present in only 3 cases. The capillaries could frequently be seen macroscopically in the nail-fold as fine lines. There is usually a sharp point of transition between the arterial and venous segments, which suggests an important difference in the structure and the response of these portions of the capillary loop to increase in the volume of the blood. The incidence of tortuous loops was related to the age of the individual rather than to the polycythemia. Capillary hemorrhages were seen in 1 patient. The response of the capillaries to the application of histamin and to mechanical stimulation was normal in 3 cases.

The absence of cardiac dilatation is striking and bears out the experimental data of Meek and Eyster on the cardiac measurements in experimentally increased volume of the blood in animals.

There is no demonstrable relationship between the systemic arterial blood pressure and the polycythemic type of increase in the volume of the blood. In only 3 patients of this series was there an elevation of systolic blood pressure and in these it was only of moderate degree. These findings agree closely with Lucas'[2] figures. The cases in his series, in which splenomegaly was present, showed fairly normal blood pressure. The diastolic pressure was not elevated proportionately, indicating that the peripheral resistance was not abnormal. It is apparent that increased viscosity and volume of the blood *per se* play a negligible part in the production of hypertension. The venous pressure, however, as would be anticipated, was increased in 2 cases in which it was tested. The capillary pressure according to the Danzer-Hooker method was normal; we could expect, however, that the application of a more accurate method, such as Carrier employed, would show at least some elevation of pressure in the venous segment.

Slight albuminuria was present in all cases, and hyaline and granular casts in most. The blood nitrogen was not elevated. The phenolsulphonephthalein excretion was definitely decreased in 2 cases. Polycythemia seems to exert no marked deleterious effect directly on the kidney.

Summary. Fourteen cases of polycythemia vera were studied in relation to the vascular readjustments to the increased volume of the circulating blood.

The total volume of the circulating blood was increased in all

cases. The average for the series was 166 cc. for each kilogram of body weight.

The viscosity of the blood was increased in all cases. The hematocrit values for the cells varied from 58 to 70 and averaged 62 per cent.

The capillaries of the nail-fold showed engorgement of the venous limb in 13 cases (92 per cent); of the arterial limb, in 4. There was complete utilization of all available capillaries of the skin.

Engorgement of the retinal veins was present in 9 cases (64 per cent). Engorgement of the skin capillaries and retinal veins disappeared when the total volume of the blood had diminished to approximately 100 to 110 cc. for each kilogram of body weight.

Determinations of skin color were made. The degree of cyanosis was determined quantitatively, and the color changes followed during the course of treatment.

Cardiac enlargement and cardiac disease were noticeably absent. The liver was slightly enlarged in 57 per cent of cases. The spleen was enlarged in every instance, and there was a distinct relationship between the splenic enlargement and the degree of increase in the total volume of the blood. There was no increase of blood pressure in polycythemia vera. The renal function was slightly impaired.

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EXPERIMENTAL CORONARY EMBOLISM.

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I. Historical. Although the importance of the coronary circulation in relation to the integrity of the heart has long been recognized,

a number of significant additions to our knowledge have been made within recent years.[8] These contributions cover the entire range of the blood supply to the heart, from the anatomic, pathologic and physiologic aspects. From the viewpoint of disturbed physiology, one of the most recent and suggestive papers is that of Bruno Kisch,[11] a student of H. E. Hering. In this paper Kisch discusses certain disturbances of cardiac function due primarily to interference with the blood supply of various areas of the heart. He emphasizes the need of exact knowledge of localization of the disturbances of the blood supply to the heart similar to the knowledge we possess of the disturbances of the blood supply to the brain. He speaks of the frequent sudden deaths of individuals suffering with advanced disease of the coronary vessels from sudden blocking of the blood supply of one of the larger coronary arteries, resulting in ventricular fibrillation—the "Sekunden-herztod" of Hering. He asks what are the results of disturbances in the coronary circulation not severe enough to produce fibrillation and death, and comments on the clinical importance of these minor disturbances resulting in a great variety of symptoms on an arteriosclerotic, infectious or other basis. He feels that this problem is best approached from the standpoint of animal experiment and cites a number of experiments with the perfused dog's heart, whereby he observed the effects of alternatingly clamping and unclamping different branches of the coronary arteries, obtaining four separate suspension curves from the heart chambers. By this means he found that clamping the left coronary artery in the perfused dog's heart resulted in alternation of the left ventricle with disturbances in the conduction system with partial or complete *A–V* block; clamping the right coronary resulted in alternation of the right ventricle but without disturbance in the conduction system. By the same experiment definite though less constant alternation of the auricles can be demonstrated, while clamping of the right coronary artery occasionally results in auricular fibrillation. Kisch comments on the fact that in dogs the conduction system is supplied for the most part by the left coronary artery while in man from the right vessel. In his conclusions he attempts to draw analogies between the results of these animal experiments and the clinical findings of angina pectoris, alternation of the heart, fibrillation of the auricles and ventricles, in patients suffering with disease of the coronary vessels.

The older methods of investigation of the coronary circulation consisted of more permanent obstruction to the bloodflow but likewise yielded valuable results. The first important contribution was made almost fifty years ago when Cohnheim and von Schulthess-Rechberg,[3] in 1881, ligated some of the larger branches of the left coronary artery in dogs, finding no change in pulse frequency and blood pressure for 30 to 40 seconds following ligation. Toward

the end of the first minute, however, the heart became definitely arrhythmic and slower and in approximately 105 seconds the apparently strongly beating heart suddenly became still, the auricle however, continuing regular pulsations. After 10 to 20 seconds of ventricular asystole, both ventricles began an active energetic fibrillation lasting 40 to 50 seconds, followed by permanent quiescence. Further contractions of the heart could not be elicited by any of various methods of stimulation and removal of the coronary ligature within 80 to 90 seconds was not effective in preventing the above sequence of events. The experimenters concluded this result was due to a particular heart poison elaborated as a result of the coronary artery closure.

Martin and Sedgwick,[12] Ferroglio and Drogoul,[7] Porter,[14] Hirsch,[9] and others, however, found variable results in repeating the above experiment, either a complete absence of stoppage of the heart or a marked prolongation of the time interval. As the most likely explanation of this variability in results, these investigators offer the physiologic importance of the anastomosis between right and left coronary arteries as well as the probable effects of mechanical trauma to the heart during the manipulation. When all mechanical trauma to the heart is controlled, the dog's heart will stand an anemia lasting from two and a half to three minutes without losing its ability to be restored with the reception of fresh normal blood.

The first study of the effects of ligating branches of the coronary artery on the electrocardiogram was made by Kahn in 1911,[10] who found a negative *T* wave after ligation of the septal artery of the dog. Smith,[17] in 1918, found in reference to the *T* wave, "a fairly constant change from the strongly positive peak to a markedly negative and then a slower return to the positive or isoelectric form" following ligation of any branch of the left coronary artery.

In addition to ligation of the coronary vessels, attempts have been made to study the effects of narrowing or partial closure of the coronary arteries, by the injections of solid materials. Panum,[13] in 1882, was the first to investigate the effects of experimental coronary embolism, by using an injection mass consisting of talcum, wax, oil and lampblack having a melting point of 40° C. Following the injection of all visible coronary vessels, the heart continued to beat intermittently for one and a half hours, thus demonstrating that the heart can withstand for a comparatively long time, partial closure of the coronary circulation.

See, Bochefontaine and Roussy,[16] in 1881, injected a suspension of lycopodium spores into the septal branch of the left and the entire right coronary artery, following which heart beats ceased in from 45 to 150 seconds. By the same method, Porter,[15] in 1896, injecting from the left carotid artery, all branches of the coronary circulation, found the heart irregular in 20 seconds, followed by a cessation of the heart beat with the development of a severe fibrillation.

Wassiliewsky[19] in 1911 injected a suspension of lycopodium spores in small portions so that only partial obliteration of the coronary circulation occurred. By this means the same animal could be injected two or three times; following the last injection the heart stopped approximately in two to five and a half minutes.

In general then the injection of lycopodium spores substantiates the results obtained by ligation. No studies of the effects of lycopodium spore injection upon the electrocardiogram have appeared in the literature.

Summarizing briefly the above observations, the results of partial or complete obstruction to the coronary circulation may be stated as follows:

(*a*) The dog's heart, several minutes after the abrupt exclusion of a considerable portion of the coronary circulation dies from want of blood (oxygen want? anemia?).

(*b*) The fatal outcome resulting from ligation of smaller-sized vessels results from accessory causes (trauma, hemorrhage, and so forth).

(*c*) The most characteristic symptom of an anemia of the heart from coronary obstruction is a more or less severe, outspoken and progressive weakness of the heart—ventricular fibrillation.

(*d*) The variability in the production of ventricular fibrillation following coronary artery obstruction is due to:

1. The size of the ligated or obstructed vessel.
2. The particular function of the area of the heart supplied by the vessel obstructed.
3. The type and degree of narcosis (more severe with morphin).
4. The extent and severity of associated hemorrhages.
5. The extent and severity of mechanical trauma.
6. The degree of local anemia (extent of collateral circulation).
7. Degree of local tissue poisons (CO_2).
8. The presence of abnormal foci of heart irritability.

II. **Purpose and Methods of Present Experiments.** The present experiments were planned with the view that the injection of minute solid particles into the coronary circulation with subsequent lodgment of these small particles (emboli) in the capillaries and arterioles, would more nearly approximate the clinical findings of coronary embolus than the ligation of larger branches. It was hoped that by the injection of a suspension of lycopodium spores, sufficient capillaries and arterioles might be occluded as to reproduce experimentally in dogs chronic interstitial myocarditis, not unlike that seen in man, the result of atheroma of the smaller capillary and precapillary vessels. We planned by this experiment to test the assertion of Aschoff, Mönckeberg and others that "practically all macroscopically visible scars of the heart muscle are the result of vessel occlusion, thrombotic or embolic in character and due to advanced atherosclerosis." We planned further, if such areas of

embolic fibrous myocarditis could be produced, to obtain electrocardiograms before and after their formation, and thus to correlate changes in the curves with the myocardial lesions.

The experiments we wish to report were carried out on a series of twelve dogs over a period of four months. A typical experiment may be described as follows: A preliminary electrocardiogram was taken as a control before interference of any sort—the dog being strapped to the operating board in the dorsal position. A preoperative hypodermic injection of ½ gr. of morphin was then given and after a short interval a second curve was taken to study the effect of the morphin. The dog was then etherized and a tracheal catheter inserted and connected to an electric blower or foot bellows. Each step in the experiment was controlled by an electrocardiogram, electrodes applied in the usual way to both fore legs and left hind leg, leads connected by distant wiring to the electrocardiograph in the Heart Station, while one of us (W. S. P.) was in constant communication by house telephone with the technician in the laboratory.

Incision of the chest was made parallel just to the left of the sternum, cutting the fourth and fifth costal cartilages and then enlarging the incision as required. As soon as the chest cavity was entered, intertracheal insufflation was started and anesthesia continued by this means until the chest was closed.

The pericardium was grasped with forceps and drawn up into the well-retracted wound. The pericardium was then split between the forceps and the heart thus lay exposed as in a sling of pericardium.

The descending anterior branch of the left coronary artery was readily discernible lying in its fatty epicardial covering over the interventricular septum. Sometimes it could be entered with no further dissection, at other times it had to be freed from the fatty tissue. We found that a hypodermic needle of the usual gauge, bent to an angle of 50 degrees, greatly facilitated the procedure.

In order to reach the posterior descending branch of the right coronary, the apex of the heart was pulled upward by gentle traction on the lower pericardium and the artery reached from behind, a certain amount of rotation being necessary.

To reach the vessels at the site of emergence from the aorta was more difficult, the fatty tissue covering the vessels was usually most marked in this location and always had to be dissected away before the artery could be identified. Furthermore, the base of the dog's heart is relatively inaccessible and the traction and rotation necessary to give good exposure often caused marked changes in the heart's rhythm.

After the experiment, the heart was allowed to drop back into the chest cavity and the pericardium closed with one or two sutures. The chest wall was closed by sutures passed directly through the cut ends of the costal cartilages and by tissue sutures. The subcutaneous tissues and skin were closed with silk or catgut and no bandages applied.

From ½ to 1 cc. of a 1 to 100 or 1 to 10 suspension of lycopodium spores in normal salt solution was injected—usually into the anterior descending branch of the left coronary artery, the vessel and its branches often being completely outlined as gray-white branches when completely filled with the suspension. After each step of the experiment and at varying intervals after the injection electrocardiograms were made—daily for a time after the operation and then usually weekly in dogs surviving for several months. At the time of death, either spontaneous or when the animal was killed, the heart was removed and studied grossly and microscopically, sections being made of all suspicious looking areas.

While some injections were made quickly and easily, others were extremely difficult and nearly impossible. This we felt was due to the small caliber of the vessels and the difficulty of introducing the needle into the vessel lumen, particularly during the rapid and at times violent contraction and movements of the heart. In general, it should be said that the entire technic is fairly difficult, particularly that portion associated with the actual injection.

III. **Results.** We shall discuss here the general results under a number of separate headings rather than to describe each experiment separately, (the details of which may be studied by those interested in the appended protocols). Of the twelve dogs operated on, five died before any attempt at coronary injection was possible—the result of the narcosis, operative trauma, hemorrhage, and so forth. Of the seven dogs actually injected, two died almost immediately following the injection, one died within 24 hours after the injection and four lived for a variable period after the injection—a period varying from two to three months. In all, 74 electrocardiographic curves were taken on the twelve animals.

(*a*) THE NORMAL ELECTROCARDIOGRAM AND THE EFFECT OF MORPHIN ON THE DOG'S HEART. The electrocardiogram of the normal dog's heart differs in no essential particulars from that of the human heart. Einthoven[4] originally called attention to the high *R* wave in Lead II and the relatively lower and equal height of all waves in Lead I. In most of our dogs the *R* wave was high in all leads although highest in Lead II. Fig. 1 shows a typical dog's heart curve under the conditions of the experiment with the dog strapped in the dorsal position to the operating board, without morphin or anesthesia of any kind. The rapid rate, 135, and the peripheral muscle tremors are easily distinguished as well as the variation in rhythm—sinus arrhythmia.

It was noted quite regularly following the subcutaneous injection of ½ gr. morphin that the heart rate became markedly slower. Electrocardiograms taken during this relative bradycardia show the rate had dropped to 50 or 60 beats per minute with a slight increase in the *P–R* interval and a noticeable heightening of *T* specially in the second and third leads (Fig. 2). It is likely that

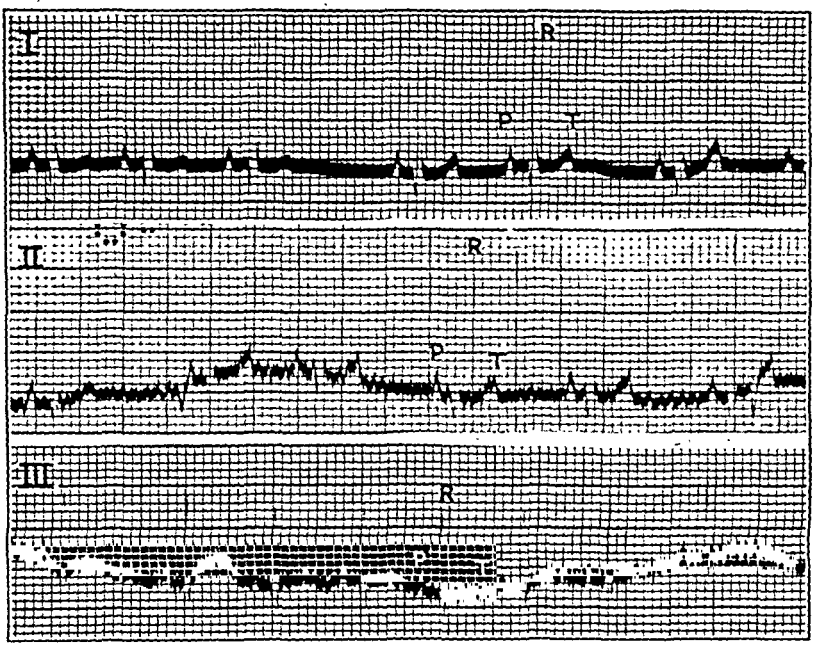


FIG. 1.—Normal curve. No morphin or anesthesia. Sinus arrhythmia. *P–R*, 0.10 second; rate, 135. Leads II and III show skeletal muscle tremors.

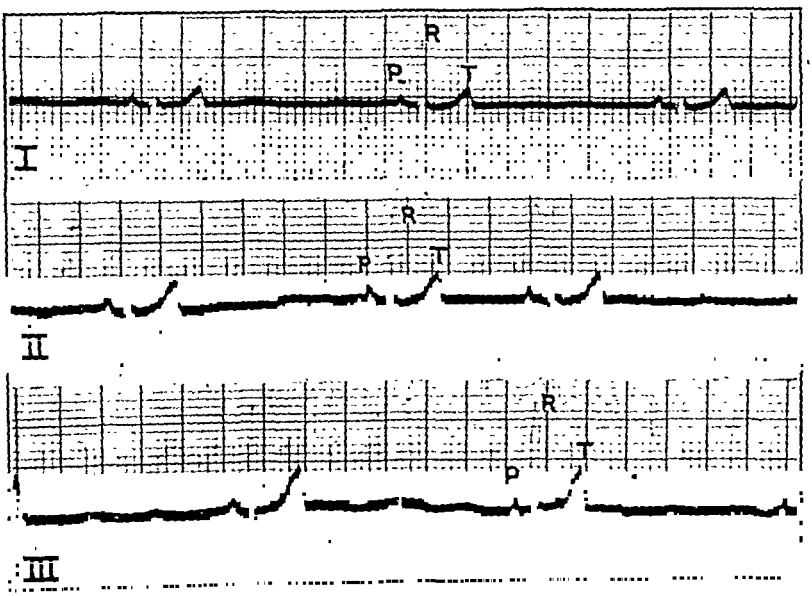


FIG. 2.—Bradycardia following injection of ½ gr. of morphin. No ether. Sinus arrhythmia. *P–R*, 0.12 second; rate, 60.

central vagus stimulation is responsible for these changes due to morphin, as described by Cohn,[2] Einthoven and Wieringer[5] and von Brücke.[1] Cohn concluded that "morphin when injected intravenously into dogs causes a disordered rhythm resulting from its action on the cardio-inhibitory center. The arrhythmia exhibits characteristics of both right and left vagus stimulation and combinations of the two."

(*b*) The Effect of Ether Narcosis on the Dog's Heart. Although considerable experimental electrocardiographic research has been done on the dog's heart and the literature contains many references to the effects of chloroform anesthesia, we have been unable to find much work on the effect of ether anesthesia on the dog's heart. As a routine in our work we took electrocardiograms immediately following complete ether anesthesia and have found a number of interesting and suggestive results. Rather regularly in all animals the heart rate increased markedly from the relative morphin bradycardia before anesthesia of 50 or 60 to a rate of 120, 130, and so forth. Not infrequently with this tachycardia the *P–R* interval was prolonged from a pre-anesthesia reading of 0.12 to 0.14 seconds to 0.18 to 0.24 seconds. In five dogs (Nos. 1, 3, 5, 6, 7) a noticeable change in the direction or height of the *T* wave was found—either an inversion, a lowered or diphasic *T* wave, or a reversal of the pre-anesthetic direction. Increase in the height of the *T* wave was noted in one dog (No. 10); no change was observed in one (No. 4) and in five dogs no data on the effects of ether was available (Nos. 2, 8, 9, 10*a*, 10*b*). A typical ether effect may be seen in Fig. 3 (dog 3) showing an inversion of *T* in all leads, prolongation of *P–R* to 0.18 to 0.24 seconds, and a tachycardia of 125. The exact significance of these findings following ether anesthesia is not clear. However, they are of considerable importance in this research in view of the effects on the *T* wave following coronary injection to be discussed later. The inversion of *T* due to ether is neither as deep nor as peaked as the initial inversion due to coronary embolus, but resembles quite closely the subsequent or secondary inversions. A more intensive experimental study of the effects of ether narcosis would seem indicated from these results.

(*c*) The Effects of the Injection of a Suspension of Lycopodium Spores into the Coronary Circulation (Experimental Coronary Embolism). The results of lycopodium spore injections into the coronary vessels may be discussed under the following divisions, the immediate results without death of the animal; the immediate results with immediate death or death within 24 hours; the later results with the dog living over 24 hours to 6 weeks, 3 months and longer.

In the first group in which the injection of the lycopodium suspension was not followed by immediate exitus of the animal, a number of bizarre and curious phenomena were observed electro-

cardiographically, showing a complete inversion of the initial ventricular complexes in all leads with occasional ventricular extrasystoles immediately following the injection of $\frac{1}{2}$ cc. of 1 to 100 suspension of spores into the anterior descending branch of the



FIG. 3.—Effects of ether anesthesia. Inversion of T in all leads. P–R, 0.18 to 0.24 second. Before anesthesia P–R was 0.14 second; rate, 125.

left coronary artery. The T wave shows no inversion but is markedly elevated. P–R is reduced to 0.08 seconds. Twenty minutes later, a second injection was followed by a drop in the heart rate from 166 to 92, the presence of both upright and inverted initial complexes with right and left ventricular extrasystoles. The transitory character of these immediate effects following injection may be judged from the fact that a curve made four and a half hours later showed practically complete disappearance of all of these abnormalities with a restoration of the normal curve as found before the experiment was started—a slight inversion of T_1 being the only abnormality. Autopsy of this dog some weeks later disclosed several small areas of epicardial thickening, no endocardial lesions. Embedded in the ventricular musculature was an area about 1 mm. in diameter composed of young, partly differentiated connective tissue, surrounded by a thin layer of denser fibrillated connective tissue, outside of which can be seen a zone containing numerous fat vacuoles with a few compressed remnants of muscle fibers.

In the second group, where death occurred within a few minutes following the injection or within the first 24 hours, still more striking and bizarre curves were obtained. In dog No. 2, following the injection of 1.25 cc. of a 1 to 10 suspension, the descending branch of left coronary vessel stood out completely filled as elevated white outlined branches. Within 10 minutes the pulse was imperceptible and death occurred in 30 minutes. The electrocardiogram showed immediately after injection complete A–V dissociation with an abnormal rapid idioventricular rhythm and a curious obliteration of R–T interval (Fig. 4). Smith[18] mentions a similar fusion of R and T waves following the injection of bichlorid of mercury and nitric acid into the region of the apex and Eppinger and Rothberger,[6] describe somewhat similar curves following the injection of sublimate or silver nitrate into the deeper layers of the left ventricle as well as following incisions into the left ventricle with severing of the branch of the bundle.*

In dog No. 3, in which 0.5 cc. of suspension was injected into the right coronary vessel, death occurred toward the end of the first 24 hours, while immediately afterward a severe tachycardia due to auricular flutter with a 2 to 1 ventricular response with short periods of ventricular tachycardia may be identified.

Considering now the third group where the dogs survived over 24 hours and from then on to 10 weeks and over we may divide these late results of coronary injection into 3 subgroups: (*a*) The results in 24 to 48 hours; (*b*) the results from the fourth to eighth

* Oppenheimer and Rothschild describe a similar fusion of the ventricular components R and T in the acute stage of myocardial damage from coronary artery closure. B. S. Oppenheimer and M. A. Rothschild, The Value of the Electrocardiogram in the Diagnosis and Prognosis of Myocardial Disease, Trans. Assn. Am. Phys., 1924, 39, 247. Krumbhaar found this also when intraventricular pressure was increased by partially clamping aorta or pulmonary artery (unpublished).

day after injection, and (c) the results from two to six weeks following injection. In dog No. 4 the curve immediately after injection showed a marked right preponderance. A curve taken 20 minutes later showed high-peaked *P* and *T* waves in Leads II and III with a tachycardia of 225. Within 48 hours after injection deeply inverted *T* waves in Leads II and III may be seen (Fig. 5), similar to those obtained by Smith following ligation. Within eight days this marked inversion of *T* was replaced by upright waves in all leads, arising prematurely from *R* in Lead II and

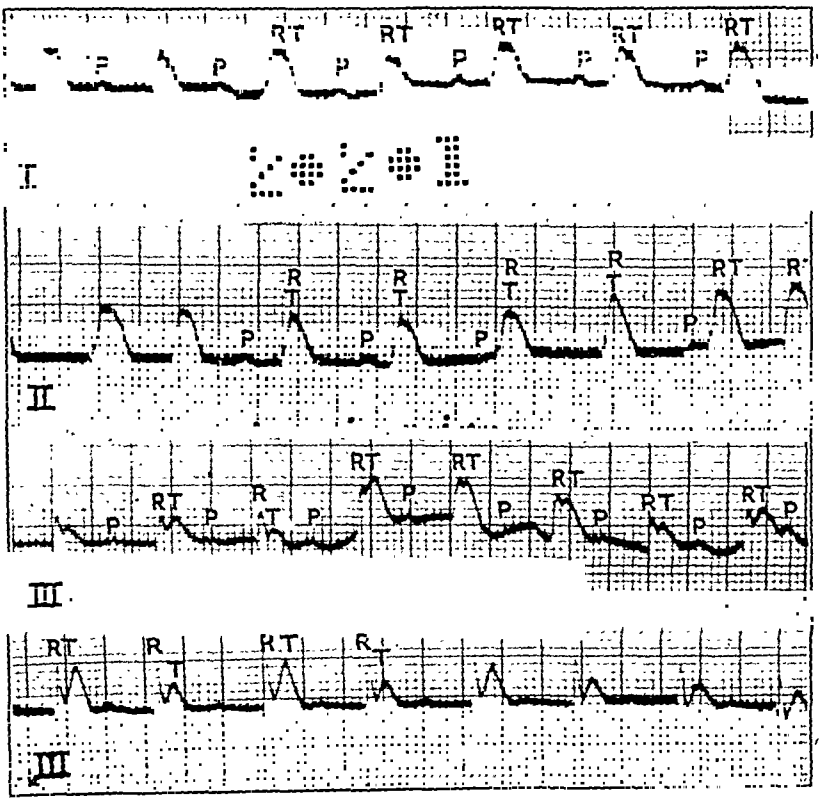


FIG. 4.—Dog No. 2. Immediately after injecting 1.25 cc. lycopodium. Complete *A–V* dissociation, auricular rate 115. Ventricular rate 135. *T* superimposed upon *Q–R–S* complex in Leads I and II, gradually emerging in Lead II.

bifurcate in Lead III. In 24 days, a right preponderance with inversion of T_1 was noted and in 57 days a secondary inversion of T_2 and T_3. Seventy-one days after injection *T* was found inverted in all leads but less deep and peaked than the inversion immediately following the injection (Fig. 6). The following day the dog was killed with chloroform, autopsy revealing an apical infarct with focal atrophy of the myocardium due to lycopodium spores (Figs. 7 and 8).

The relatively insignificant disturbance of the cardiac mechanism of dog No. 4 contrasts strikingly with the profound disturbance found in dog No. 5. Immediately following the injection of 2 cc. lycopodium suspension the beginning of Lead I shows a short period of comparatively normal mechanism followed quickly by a period of right bundle branch block interrupted by short periods of auricular fibrillation and flutter. Lead II shows periods of normal mechanism interrupted by periods of ventricular tachycardia and groups of

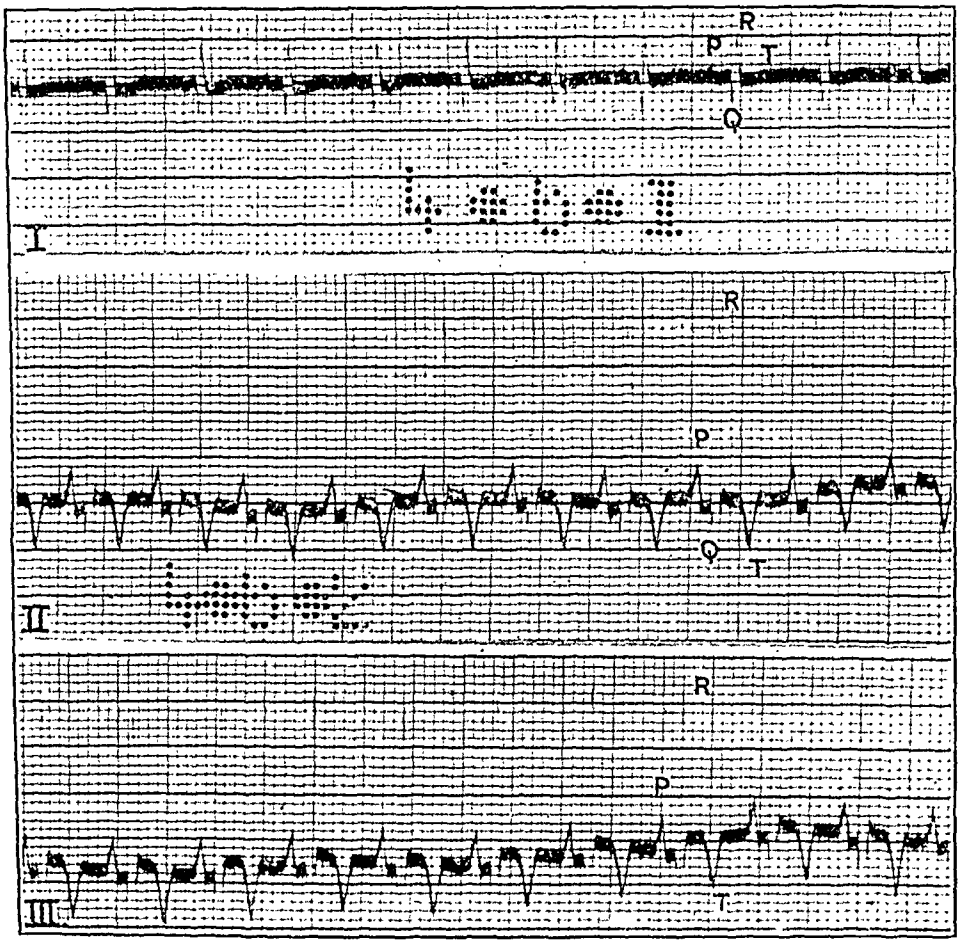


FIG. 5.—Dog No. 4. Forty-eight hours after injection. *T* deeply inverted in Leads II and III. *P* abnormally high in II and III. *P–R*, 0.08; rate, 165.

ventricular extrasystoles arising in or near the *A–V* node. This later focus finally dominated the mechanism. Lead III shows fairly normal mechanism interrupted by extrasystoles arising in or near the *A–V* node.

Twenty minutes after injection one finds an essentially normal mechanism. Within 24 hours deep inversion of *T* in all leads was found. Seventeen days after injection inversion of T_1 still persisted (Fig. 9). From then on, on various occasions (curves taken weekly

for six weeks), return to upright *T* waves with secondary and tertiary inversion of *T* in various leads occurred until the seventy-third day when the dog was killed. Autopsy revealed the myocardium and endocardium of the left ventricular surface of the apex and interventricular septum markedly fibrosed while microscopically a chronic interstitial myocarditis of the apical portion due to occlusion of arteries by lycopodium spores was found (Fig. 10).

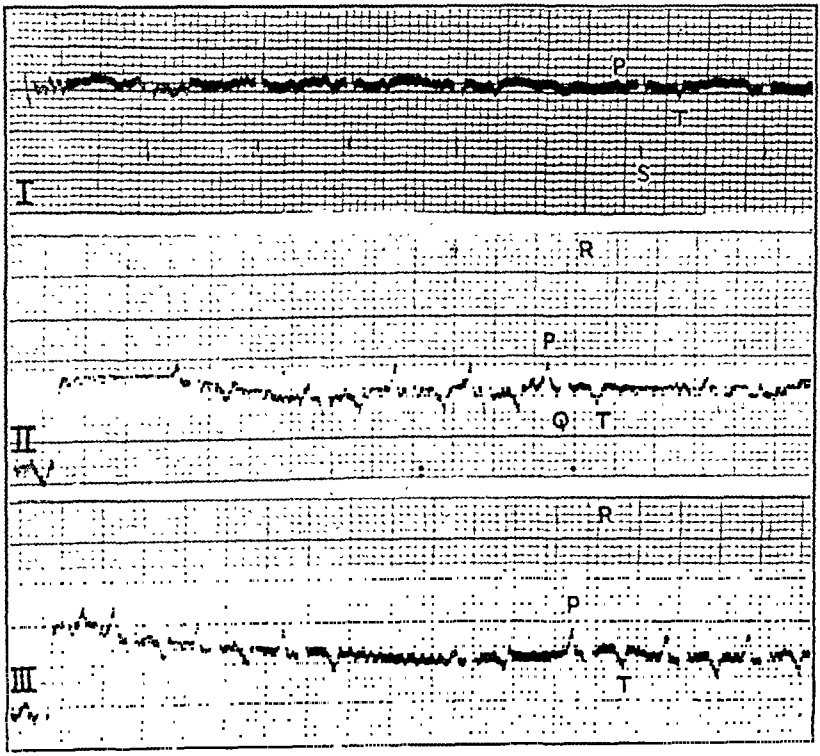


FIG. 6.—Dog No. 4. Seventy-one days after injection. Right ventricular preponderance. Inversion of *T* in all leads. Apparent migration of pacemaker, with occasional block between origin of stimulus and auricular conduction system. *P–R*, 0.08 to 0.12 second; rate, 105.

Although dog No. 7 failed to show any striking changes immediately following injection, the curve taken 24 hours later showed the typical deep-peaked inversion of *T* referred to previously. Four and again eight days later *T* became upright only to again undergo a secondary inversion on the forty-third day (Fig. 11), at this time much less pronounced than the primary inversion. Autopsy revealed many recent subendocardial hemorrhages as well as some white scarring of the endocardium of the left ventricle. Microscopically beneath the endocardium and more deeply within the myocardium of the apex of the heart where the small pale areas

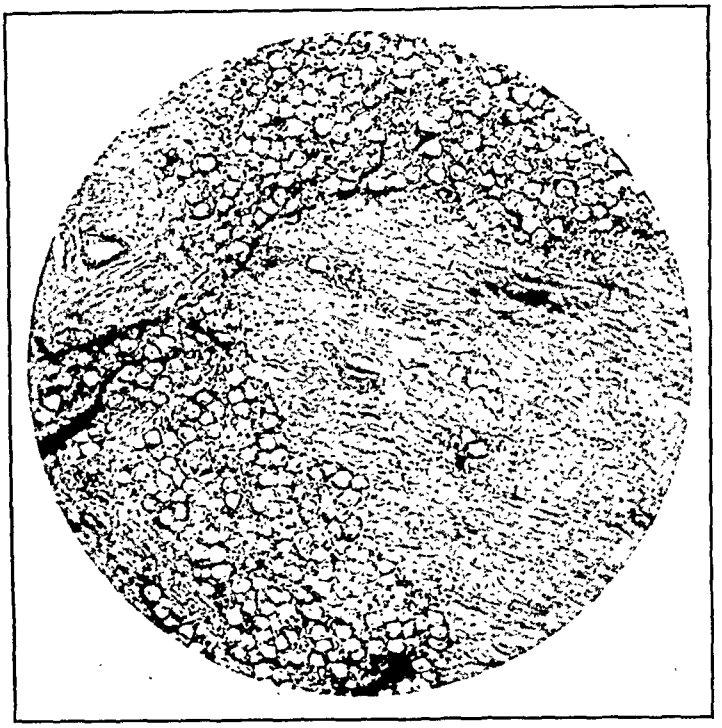


FIG. 7, Dog 4.—Apical infarct with focal atrophy of the myocardium with areas of closely packed lycopodium spores. EKG. showed primary and secondary inversion of *T* in all leads (Figs. 5 and 6).



FIG. 8, Dog 4.—Myocardial degeneration with small number of lycopodium spores.

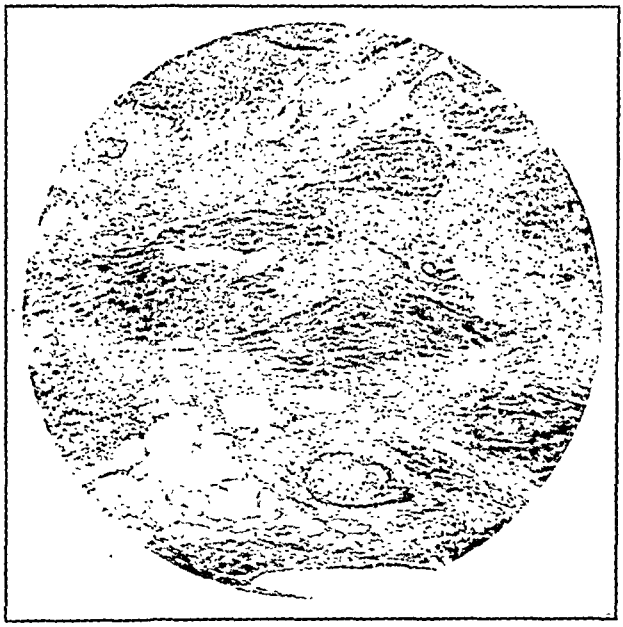


FIG. 10, Dog 5.—Chronic interstitial myocarditis (myocardium being replaced by broad bands of fibrous tissue) following occlusion of arteries by lycopodium spores. Note vessels filled with spores. EKG. showed primary and secondary inversion of *T* in all leads.

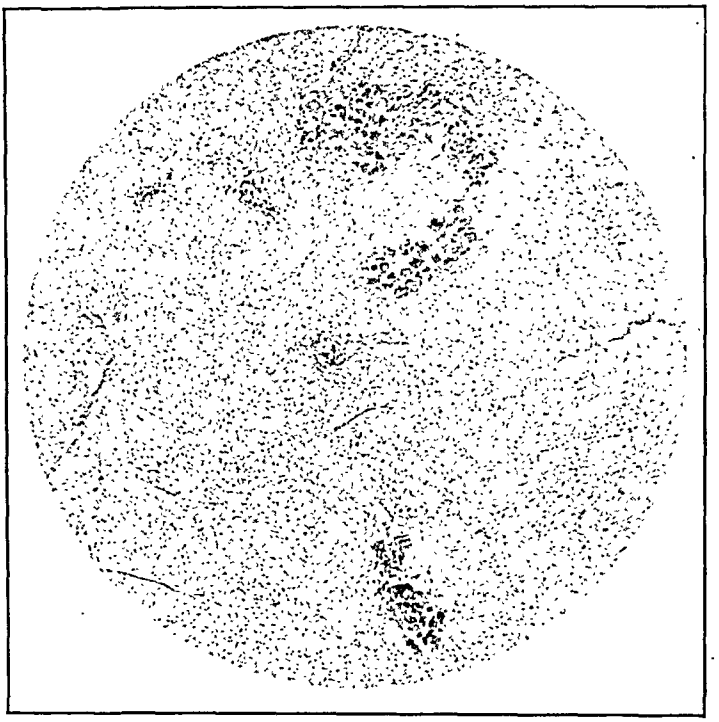


FIG. 12, Dog 7.—Areas of necrotic muscle fibers (focal necrosis) and calcification of myocardium. EKG. showed primary and secondary inversion of *T* (Fig. 11).

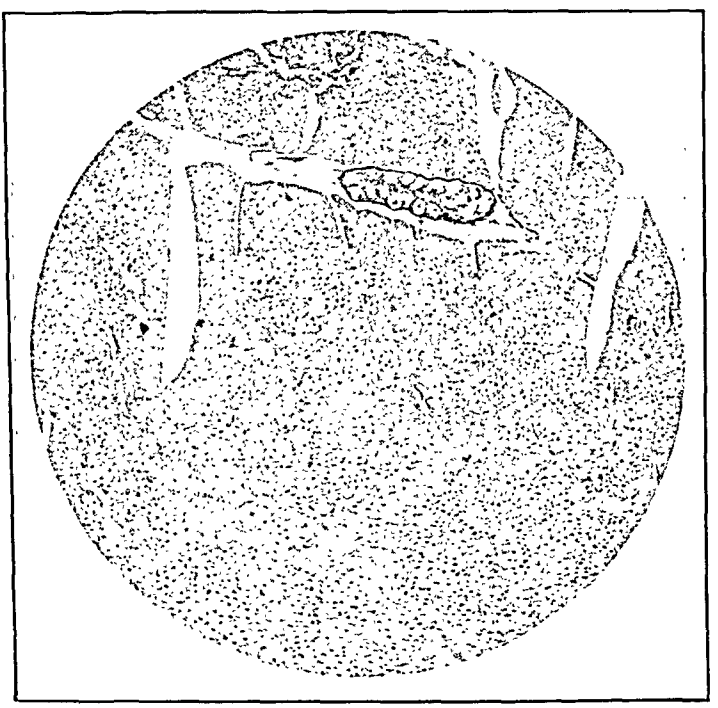


FIG. 13, Dog 10.—Acute cloudy swelling and fragmentation of heart muscle. EKG. showed ventricular fibrillation.

were visible in the gross, were numerous small areas composed of necrotic muscle fibers which stain deep blue because of calcium infiltration (Fig. 12). No lycopodium spores are visible.

One dog, No. 10, dying almost immediately following the injection from ventricular fibrillation, we wish to mention briefly. Following the injection into the anterior descending branch of the left coronary artery, the heart went into immediate fibrillation and within a few minutes the animal was dead. Autopsy showed a dilated heart with arteries pale, veins distended. Microscopic examination showed acute cloudy swelling and fragmentation of the heart muscle with congestion of myocardial vessels and many vessels packed with spores (Fig. 13).

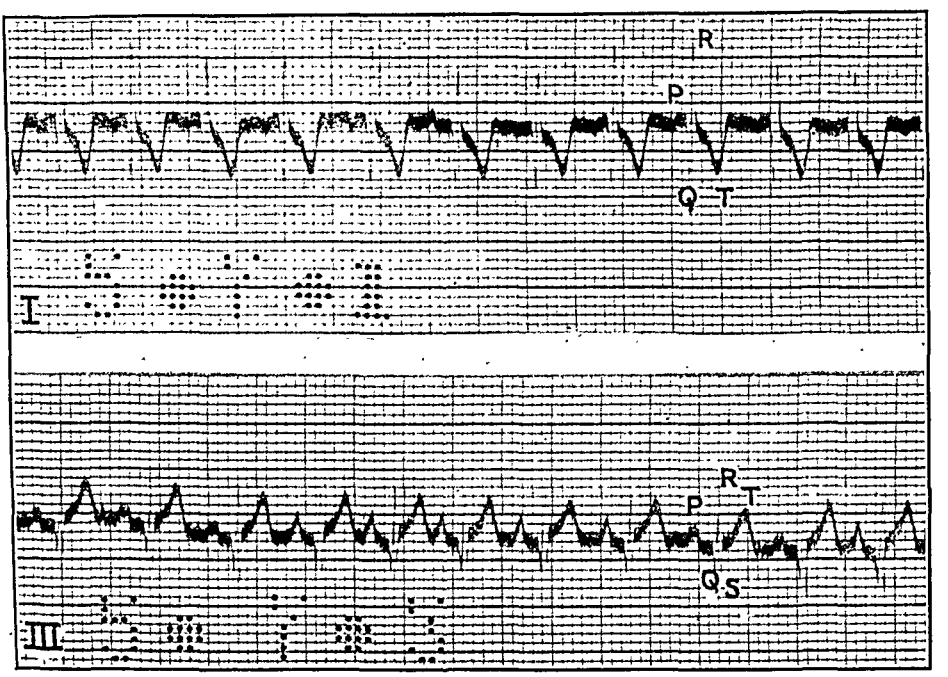


FIG. 9.—Dog No. 5. Seventeen days after injection. Inversion of *T* in I. Migration of pacemaker suggested by differences in *P*. *P–R*, 0.12 second; rate, 195.

IV. **Discussion.** Morphin administered hypodermically to dogs in $\frac{1}{2}$-gr. doses causes a marked slowing (bradycardia) to a rate of 50 or 60 heart beats per minute. This slowing is probably due to central stimulation of the cardioinhibitory center as described by Einthoven and Wieringer, Cohn and others.

Ether narcosis in dogs causes quite regularly an inversion, decrease in height, diphasic contour, or change in the previous direction of the *T* wave of the electrocardiogram. It likewise increases markedly the heart rate from the morphin bradycardia of 60 before narcosis to a tachycardia of 120 to 130, meanwhile prolonging the *P–R*

interval to 0.18 to 0.24 seconds. The explanation of these effects from ether is not clear but suggests the need of further experimental work.

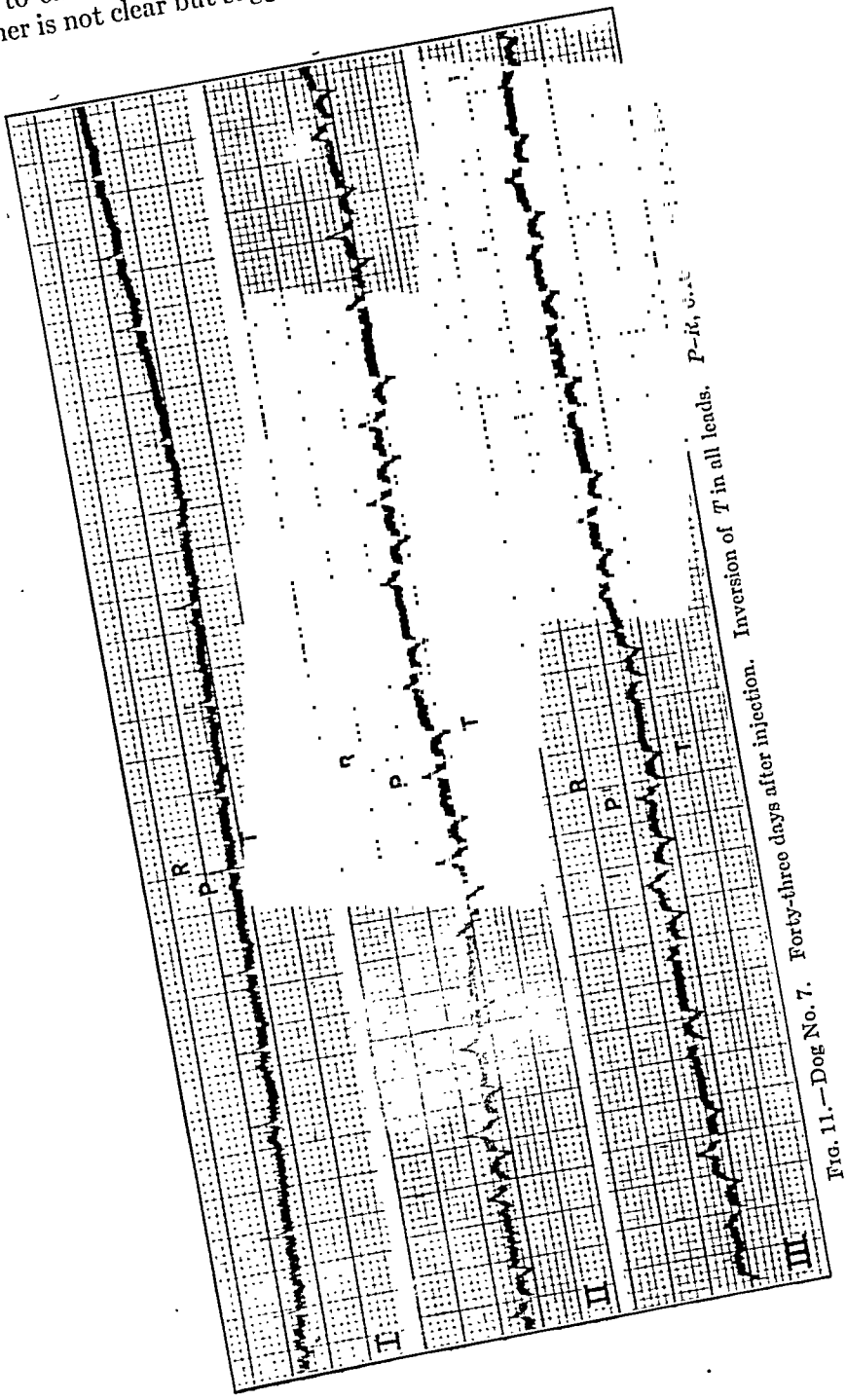


FIG. 11.—Dog No. 7. Forty-three days after injection. Inversion of T in all leads. P–R,

The results of the injection of a suspension of lycopodium spores in the coronary circulation (experimental coronary embolism) vary depending on the size and number of vessels obliterated, the size and physiologic importance of the resultant ischemic area, as well as the rapidity of the establishment of collateral circulation. Relatively widespread and sudden obliteration of arterioles and capillaries from massive lycopodium spore injections results in immediate death of the animal, the electrocardiogram showing complete *A–V* dissociation, obliteration of the *R–T* interval, auricular flutter or ventricular fibrillation. The injection of a smaller number of spores with the involvement of smaller areas of the heart is compatible with complete recovery of the animal, the electrocardiograms in such dogs showing variously, inversion of initial ventricular complexes, right ventricular preponderance, nodal rhythm, ventricular extrasystoles, with primary and secondary inversion of the *T* wave. The apical areas of the hearts of these dogs show typical chronic interstitial myocarditis scarcely to be distinguished from that occurring in man as a result of atherosclerotic obliteration of the smaller coronary vessels.

When the injections missed the lumen of the vessel to any considerable extent, no permanent change in the electrocardiogram (*T* wave) was found, although strange and curious findings were noted transitorily. At autopsy the lesions noticed were epicardial and not confined to the apex. It is probable that the slight hemorrhage and trauma incidental to the injection and manipulation of the heart must be held responsible for these transient bizarre phenomena.

When massive injections were followed promptly by death of the animal, ventricular fibrillation was found in the most sudden death, exitus occurring almost at once following the injection; the dog dying within 30 minutes showed complete *A–V* dissociation with obliteration of the *R T* interval, while the animal dying within the first 24 hours showed a severe tachycardia with auricular flutter.

In the dogs surviving for days and weeks following the injection the changes in the *T* wave are at once the most interesting and the most difficult to interpret. In most instances inversion of *T* did not occur immediately, curves taken 20 minutes after the injection showing a physiologic curve. Within 24 to 48 hours, however, all showed the deep-peaked inversion, which again about the eighth day became upright. From then on at varying intervals secondary and tertiary inversions and return to the upright position occurred, each inversion, however, being less pronounced and deep than the preceding. Quite regularly the dogs showing the most marked inversion showed at autopsy infarction in the apical region of the left ventricle. While much work and considerable difference of opinion exist as to the significance of the inversion of *T*, and while it is generally felt that *T* is a relatively labile wave, easily influenced

by many procedures and by lesions in various areas of the heart, this work lends support to the view that inversion of *T* is due to an area of infarction in the apical region of the left ventricle and that its direction is due to prolongation or delay of activity at the apex in relation to final activity at the base. Further, the degree and configuration of the inversion varies with the cause, witness the type of inversion due to ether with that following infarction. Assuming in the latter, that inversion is due to structural changes at the apex, it is difficult to understand the changes in direction from day to day and week to week, tempting one to speculate on the probable parallel changes in pathology as healing goes on from the possibly initial ischemia, cloudy swelling and fragmentation, to possibly secondary congestion, edema or hemorrhage, with inflammatory reaction and finally newly-formed connective tissue and fibrosis.

Conclusions. 1. Hypodermic administration of morphin to dogs causes marked bradycardia, probably due to central stimulation of the cardio-inhibitory center as described by Einthoven and Wieringer, Cohn and others.

2. Ether narcosis in dogs causes inversion and other changes in the *T* wave of the electrocardiogram, acceleration of the heart rate and prolongation of the *P–R* interval.

3. Injection of a suspension of lycopodium spores into the coronary circulation of dogs (experimental coronary embolism) causes:

(*a*) Death at once, or within 24 hours, depending on the amount of the injection and the size of the resulting infarct, the animals dying immediately, showing ventricular fibrillation; those dying within 30 minutes, complete *A–V* dissociation with obliteration of the *R–T* interval; those within 24 hours, tachycardia from auricular flutter, with cloudy swelling and fragmentation of the myocardium, and vessels distended with spores.

(*b*) Changes in the electrocardiogram compatible with life, such as inversion of initial complexes, right preponderance, nodal rhythm, ventricular extrasystoles, ventricular tachycardia.

(*c*) Primary, secondary and tertiary inversion of the *T* wave of dogs surviving the injection for two to three months, the heart at autopsy showing quite regularly infarction (fibrosis) of the apex of the left ventricle with vessels filled with spores, with typical chronic interstitial myocarditis scarcely to be distinguished from that occurring in man, the result of atherosclerotic obliteration of the smaller coronary vessels.

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SPONTANEOUS RUPTURE OF THE HEART.*

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SPONTANEOUS rupture of the heart is regarded as of infrequent occurrence, and is seldom recorded in civil hospital records. In coroners' services and in institutions for the insane such instances are more frequently found. They are undoubtedly being missed in private hospital practice.

Numerous individual and collected reports of spontaneous rupture of the heart may be found, yet a comprehensive study of this subject is lacking in the English literature. We have gathered 320 instances from the literature and have added 5 from our own material, classifying the symptoms according to their incidence and giving particular attention to the etiology and pathology. We will show that this condition most frequently follows obstruction of a coronary artery. Coronary thrombosis invariably results in infarction of that portion of the heart wall supplied by the obstructed vessel. Proper management of such a patient will aid in preventing a rupture of the infarcted area.

Etiology. The age incidence and the more common predisposing factors resulting in spontaneous heart rupture in 245 instances in which the age was mentioned are given in Table I.

* A paper on this subject will also be found in this Journal, 1925, **170**, 828.

TABLE I.

Age.	Number.	Predisposing cause.
Birth to 10 years . . .	1 (aged 5 years)	Syphilitic myocarditis.[18]
10 to 30 " . . .	1 (aged 22 ")	Gumma of heart.[4]
30 to 50 " . . .	1 (aged 35 ")	Obliterative endarteritis of the coronary arteries.[6]
	2 (aged 30 " and 36 ")	Sclerosis of the coronary arteries and myomalacia cordis.[12,19]
	1 (aged 36 ")	Ulcerative endocarditis.[1]
	1 (aged 45 ")	Syphilitic myocarditis.[4]
50 to 60 " . . .	10	Myomalacia cordis.
60 and beyond . . .	209	Myomalacia cordis most frequently recorded.
80 to 90 years . . .	4	Myomalacia cordis.

The two sexes are nearly equally divided in Quain's review of 100 examples.[3] In 218 instances from our group, 122 were males and 96 females.

The common predisposing cause which was responsible for 226 of the 325 ruptures from which this study was made was an embolism, or an atheromatous sclerosis and thrombus formation in a coronary artery or arteries, resulting in an anemic infarct. The condition of the coronary arteries was not stated in 93 instances. Undoubtedly some of these would have presented changes, had they been looked for. Anemic infarct has been termed myomalacia cordis in many of the reported instances. Other unusual causes were, ulcerative endocarditis,[1, 2] abscess of the heart wall[3] and gumma of the heart wall.[4]

Exciting factors are not necessary. Mental strain, extreme emotion and physical exertion have been stated by some as present at the time of rupture. In our study, we found that more frequently there was no exciting factor and that rupture occurred while the patient was at rest.

A large proportion of the reported examples of heart rupture occurred in the insane. We have found no explanation of this. Since the usual cause is primarily arteriosclerosis, one might conjecture that the manner of living, sedentary habits and often irrational diet of insane patients predispose to arterial lesions. Statistics on the incidence of arteriosclerosis in the insane bear this out.

Pathology. Spontaneous heart rupture does not occur without lesion of the myocardium. The pathological changes may only be detected by microscopic study. Given a weakened heart wall, any condition which raises the blood pressure in such a chamber favors its rupture.[1] Stenosis of the tricuspid valves or obstruction in the pulmonary circulation favors rupture of the right heart. Aortic stenosis, mitral stenosis or increased arterial pressure favors a rupture of the left heart, and yet these are theoretical reasons since very few ruptured hearts present such valvular changes.

Sclerosis of the coronary arteries was found in a high percentage of instances in which rupture of the heart wall occurred.

The ruptures may be single or multiple, complete or incomplete, direct or indirect. They may vary in size from a few millimeters to 4 or 5 cm. They may be located in any area of the heart wall. Table II gives the anatomic locations.

TABLE II.

	Examples.
Anterior wall, 66 per cent Posterior wall 34 per cent	115
Left ventricle	253
Right ventricle	35
Right auricle	16
Left auricle	4
Interventricular septum	1

In unusual instances ruptures may be multiple. In 3 instances two separate ruptures were found.[1,5,6] In 2 other instances[7,8] one channel had an exit through two or three slits in the epicardium. In a recent autopsy in this hospital, three linear tears through the epicardium were located over a large healed infarct in the left ventricle.

The process of atherosclerosis of the coronary arteries, as of other arteries, consists first of a swelling of the intercellular cement substance in the intima. This is followed by a swelling of the intimal cells themselves, and a deposition of hyaline material resulting in a thickening of the intima. Lipoid substances from the blood stream are deposited in these areas in increasing amounts until an "asphyxiation necrosis" results.[10] This is followed by the formation of calcium soaps. By this time the endothelial lining of the intima has broken through and on the exposed atheromatous ulcer a thrombus forms which increases progressively in size until the narrowed lumen is entirely obliterated, depriving the distal heart muscle of its blood supply. An ischemic infarct in the heart muscle results.[9] Various names are given in the literature to this area of ischemic necrosis, for example, myomalacia cordis, coagulation necrosis, fatty degeneration and anemic infarct. Each of these is descriptive of some phase of the process of necrosis and all apply to the condition of ischemic infarct.

As soon as the blood supply of a given area of the heart wall becomes insufficient, degeneration of the heart muscle takes place. The cells become swollen, lose their striations and appear finely granular. They finally lose their cell outline and deep staining granules and pyknotic nuclei remain. In the degenerated cells are accumulated globules of fat so that the process is described by Quain as fatty degeneration. During this degenerative process, according to MacCallum, a ferment is produced which coagulates the intracellular and extracellular fluids so that a firm coagulum

is formed in this area.[11] Through phagocytic ferment action the coagulum is finally softened and absorbed. The heart wall becomes thinned and is weakened so that an aneurysm may result. The blood from the heart chamber forces its way through the softened heart muscle dissecting a ragged, irregularly-shaped channel. A cavity is thus produced within the heart wall which is filled with necrotic muscle tissue and clotted blood. Rupture finally occurs through a linear slit in the epicardium extending parallel to the long axis of the heart.

Gross Pathology. The heart is usually found to be hypertrophied, due to the fact that many instances are associated with hypertension and generalized arteriosclerosis. The cut surface of the myocardium is pale yellow in color with a greasy, glistening appearance. A colored zone of hemorrhagic infiltration into the necrotic muscle, 1 to 2 cm. in width, surrounds the rupture. There is a thinning of the wall in this region, which is soft and friable and punctures easily.

The pericardial sac is distended with 300 to 500 cc. of fluid and clotted blood. In an unusual instance the pericardium was adherent to the site of rupture and rupture took place into the mediastinum.[12] Instances are mentioned in which complete rupture was prevented by an adherent pericardium.

Microscopic Pathology. Each of our examples had an obliterative thrombosis of a coronary artery. Atheromatous degeneration was also found in the smaller branches, with resulting partial obliteration. Near the ruptured area the muscle cells presented various stages of degeneration. In some this was manifested only by a yellow-brown pigment surrounding the nuclei and by fading of the striations. In other areas, only small fragments of muscle cells remained. These had pyknotic nuclei, no striations, and were imbedded in a fibrous tissue network containing leukocytes and plasma cells. In all sections examined, wandering cells infiltrated the involved area and small areas of round-cell infiltration were seen. At the margin of the rupture an organized thrombus was attached to the necrotic heart muscle.

Myocarditis. All carefully studied instances of spontaneous heart rupture occurring under thirty years of age have been due to syphilitic myocarditis. Several instances of spontaneous rupture were mentioned in the literature in which no gross myocardial changes were evident. Inasmuch as syphilitic myocarditis may present no gross pathology, it seems plausible that a certain number of these instances, if studied microscopically, might come under this group.

Warthin has described certain pathognomonic microscopic characteristics in congenital syphilis of the myocardium.[13] The smaller arteries have a lymphocyte, plasma cell, collar infiltration. Proliferating interstitial fibroblasts and groups of large, pale

staining, irregular-sized endothelial cells and round cells are characteristic. Spirochetes, diffuse and numerous, may be found by special staining methods. There are areas of coagulation necrosis and fatty degeneration of the heart muscle in which no fibrosis or spirochetes are found. Some of the smaller vessels show endothelial cells proliferating in their walls after filling the lumen. The adventitia undergoes fibrous thickening and the perivascular tissues present fibrous hyperplasia and lymphocyte and plasma-cell infiltration. The interstitial changes are more marked than the vascular changes.

St. George[4] briefly describes a rupture due to a gumma of the anterior wall of the left ventricle. No other instance was found in the literature. We have not been able to find an instance of echinococcus cyst or tumor of the heart wall causing rupture. These were mentioned frequently in the literature as predisposing causes.

Symptomatology. In our study of 325 examples of ruptured heart wall, less than 25 per cent gave a history suggesting previous heart disease. These fell into one of two groups: The larger group gave a history of dyspnea and rapid heart action on exertion, cyanosis and varying degrees of precordial distress, which varied from mild precordial discomfort, leaving promptly upon the cessation of exertion, to severe attacks of pain with radiations characteristic of angina.

The second, and smaller group gave a history of symptoms referable to disturbances below the diaphragm, often gastric in nature. Epigastric pain was most often noted.[14] This pain had no relation to the ingestion of food and was not relieved by vomiting when vomiting did occur. The pain usually persisted in the upper part of the abdomen. Radiation to the right or left subscapular region was noted frequently. Radiation to the right subscapular region, together with epigastric tenderness and vomiting, occasionally led to the diagnosis of gall bladder disease.

Approximately 75 per cent of the instances of ruptured heart wall gave no history suggesting heart disease previous to the time of final illness. These patients fell again into two groups: In only a comparatively few instances was death without premonitory warning. These patients sustained sudden collapse, cyanosis and coma. The heart action and respirations stopped within one to two minutes.

A very large majority of patients lived from a few hours to two days after the onset of the final illness. In this group the most common symptom was a severe, persistent, tearing pain in the precordium or beneath the sternum. This pain, in an occasional patient, radiated down the left arm or into the neck. The skin was pale. Drops of perspiration stood out on the face and body. The pulse was usually rapid, often irregular, and became progressively weaker. In a few instances the pulse was slow. Many

patients had temperatures from 99° to 101°. From these symptoms, which were indicative of a desperate situation, the patient frequently rallied temporarily. Death usually followed suddenly within a few hours to two days in a manner previously described. References are made to one patient living eight days and one living seventeen days after rupture occurred.[15,16] From descriptions of the symptomatology and the pathologic processes in these instances, we believe this not to be the case. In these patients we believe that the primary symptoms were due to coronary thrombosis which in turn was followed by infarction of the myocardium. When rupture finally does occur, death ensues within a few minutes.

A careful survey of the histories of many of the reported instances of ruptured heart leads one to believe that acute coronary obstruction did occur. The primary symptoms were due to this accident. The processes of infarction in the area in which nutrition was interfered with through obstruction to its arterial supply of blood, resulted in a marked weakening of the heart wall, through which the blood forced its way.

The physical findings, either at the time of acute coronary obstruction or at the time of rupture, may be negative. The heart may dilate. A pericardial friction rub may develop. Cardiac irregularities occur, due to auricular fibrillation, extrasystoles or heart block (an observation by Dr. Herrick). The heart sounds thus become faint even before rupture occurs.[31] In one instance the murmur caused by the passage of blood through the ruptured heart wall was heard and a clinical diagnosis of this condition made.[33] This was corroborated by necropsy. The increase in size of the pericardial sac as it becomes filled with blood may be detected by the extension of dulness to the left beyond the nipple line.

Diagnosis. The diagnosis of rupture of the heart wall resolves itself into a primary diagnosis of obstruction of a coronary artery, of which we found clinical or pathological evidence in 226 of the 325 instances making up this study.

The recognition of coronary obstruction has been materially aided as the result of a paper published by Dr. J. B. Herrick[17] in 1919 in which the clinical features were carefully discussed. His classification of this condition outlined three groups: (1) Instances of sudden death; (2) instances of death within a few minutes to a few hours; (3) instances in which death was delayed to days or weeks. The material from which our study was made fits equally well into this classification, as it should, since much of it has the same pathologic basis.

The statement has frequently been made that rupture of the heart can only be ascertained by autopsy. In this connection Dr. Herrick's discussion of acute coronary obstruction is apropos: "As in so many other conditions, the first essential is to think of this condition as a possibility and to rid the mind of the notion that

such a diagnosis is possible only at necropsy." The first step will then be to diagnose coronary obstruction. Having made this diagnosis, rupture of the heart wall through the infarcted area becomes a matter of prognosis if the patient still lives, and a possibility to have in mind if the patient dies suddenly.

Treatment. The early recognition of acute coronary obstruction is of vital importance, since it permits of measures that may prevent rupture of the area of infarction. The pain should be controlled by adequate doses of morphin, hypodermically. Since increased energy of the heart favors rupture, it is better to avoid cardiac stimulation by drugs. Absolute rest in bed for a long period of time should be insisted upon to allow healing of the infarct. After rupture has occurred, death follows so quickly that treatment cannot be instituted. Suture of the rupture has been suggested, but must be an impossible procedure because of immediate collapse.

Examples. Our first example is an instance of thrombosis of the coronary artery occurring twenty-four hours before death. Rupture of the infarct undoubtedly occurred at about the time of admission to the hospital.

F. H., a white male aged seventy-four years, was admitted to the Santa Barbara Cottage Hospital in collapse. He was extremely cyanotic. The extremities were cold. The respirations were of the Cheyne-Stokes type. The pulse was imperceptible. He died within ten minutes.

Twenty-four hours before, he had consulted a physician on account of sudden precordial distress, great weakness, dizziness and rapid heart action. The physician had advised him to go to bed. This he did, but arose early the next morning and started in his automobile for a destination 100 miles distant. His precordial distress increased in severity and an hour before admission to the hospital he was forced to turn the wheel over to a companion who drove him to the hospital. He is said to have suffered excruciating pain in the chest during this last hour.

Postmortem examination revealed a pericardial sac distended with clotted blood. On the posterior surface of the left ventricle, 4 cm. from the septal line and 6 cm. from the apex, was a linear tear in the heart muscle, 2 mm. in length, through which a probe could be passed into the ventricular cavity. The muscle tissue surrounding the aperture—an area 3.5 cm. in diameter, was soft, friable, dark in color and infiltrated with blood. The inner aperture was covered by an organized blood clot. The aorta, aortic valves, orifices of the coronary arteries and intima of the coronary arteries were markedly sclerotic. The left branch of the anterior coronary artery was completely occluded 2 cm. above the site of rupture by a thrombus. The heart weighed 380 gm. The muscle of the left ventricle measured 2.5 cm. in thickness. All other valves than the aortic were normal.

Our second example is one of rupture of the heart occurring without premonitory symptoms having been noted.

Mr. Charles S., a private patient of Dr. H. O. Koefod, had suffered from gout for forty years. He was eighty-four years of age. For several weeks prior to death he was bedridden. During this period the pulse was normal in rate, character and regularity. The radial arteries were markedly sclerotic. The blood pressure was systolic, 140; diastolic, 90. The patient had had no symptoms referable directly to the heart. After a half hour's absence the nurse returned and found him dead.

Postmortem examination revealed a hemopericardium. There was a linear tear through the myocardium of the left ventricle at the apex. The tissue surrounding the aperture was necrotic and measured only 2 mm. in thickness. Surrounding the inner aperture was an organized blood clot. The cause of the infarct was a thrombus in the anterior coronary artery 1 cm. above the site of rupture. The aorta, aortic valves and coronary arteries were sclerotic. The muscle of the left ventricle measured 2 cm. in thickness. The heart weighed 400 gm.

Our third example is again of the type in which premonitory symptoms were not noted.

Mrs. M. A., an elderly white woman, was admitted to the White Memorial Hospital, in Los Angeles, on February 14, 1924. She had a hypertension, her pressure being: systolic, 220; diastolic, 130. The left border of the heart was 1 cm. beyond the nipple line. The urine contained a trace of albumin and sugar. The blood sugar was 0.23 per cent. She did not complain of any symptoms referable to heart disease. On February 21 the patient complained of pain and a sense of fullness in the epigastrium. On February 22 she again complained of this fullness, which was relieved by soda. On February 23 the patient felt well. At 3 P.M. she went to the bathroom and returned to bed, making no complaint. At 6 P.M. she was found dead in bed with no evidence of a struggle.

Postmortem examination revealed a pericardial sac distended with blood. A tear 1 cm. in length was found through the anterior wall of the right ventricle, close to its apex. The muscle surrounding the tear was infiltrated with blood for a distance of 1.5 cm. surrounding the rupture. The aorta and aortic valves were sclerotic. The condition of the coronary arteries was not stated. The muscle of the left ventricle was increased in thickness.

Our fourth example illustrates a thrombosis occurring seven days before rupture of the heart wall.

Mr. S., aged sixty-eight years, was a private patient of Dr. L. W. Hotchkiss in the Santa Barbara Cottage Hospital. He had undergone a prostatectomy and his surgical recovery was progressing uneventfully. He was suddenly seized with tearing precordial

pain. He broke into a perspiration, the pulse became rapid and weak. Within twenty-four hours a friction rub was audible over the precordium. Marked tenderness persisted over the entire precordium. On the seventh day following the onset of this precordial disturbance, the patient complained again of agonizing pain about the left nipple and was dead within one minute's time.

Postmortem examination revealed a linear longitudinal tear in the anterior wall of the left ventricle 2 cm. in length, situated 1 cm. from the septum and 6 cm. from the apex. Surrounding the aperture was an area of necrotic muscle 3 cm. in diameter. This necrotic area was 5 mm. in thickness. The right branch of the anterior coronary artery was completely occluded by a thrombus. There was present only a moderate sclerosis of the root of the aorta and of the aortic valves. The coronary arteries presented a more advanced degree of sclerosis. The muscle of the left ventricle was 1.5 cm. in thickness. The heart weighed 270 gm. No other abnormality was seen.

Our fifth example is a specimen obtained from Dr. A. M. Moody of San Francisco. The clinical history of this patient was not available.

Examination of the heart revealed a linear longitudinal tear 1 cm. in length in the posterior wall of the left ventricle 3 cm. from the septum and 5 cm. from the apex. The external aperture opened into a cavity 1.5 cm. in diameter surrounded by an organized blood clot and necrotic muscle. The inner aperture was circular and measured 1.5 cm. in diameter. Surrounding the aperture was an area of necrotic muscle 1 to 2 cm. in width; 2 cm. above the site of rupture the posterior coronary artery was occluded by a thrombus. The root of the aorta, the aortic valves and the coronary arteries were markedly sclerotic. The muscle of the left ventricle measured 2.3 cm. in thickness. The heart weighed 340 gm. No other abnormality was seen.

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SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD AND PERNICIOUS ANEMIA.

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Pernicious anemia, as a clinical entity, was described by Addison in 1855 and by Biermer in 1868 with a lucidity which has never been excelled. While Addison called it idiopathic, Biermer gave

it the name pernicious anemia. H. C. Wood, Cohnheim, Minnich and others developed our knowledge in regard to the pathogenesis of the bone-marrow lesions and the changes in the blood film. The clinical picture, lemon-tinted skin, whitish mucous membranes, Hunter's glossopharyngitis, gastric achylia, diarrhea or constipation, is well known and needs no further comment. The blood film with its anisocytosis, poikilocytosis, decreased platelets, its embryonal cells such as megaloblasts, and the abnormal color index over 1, as well as the icteric index (J. Evans) of the blood serum over 11 and the bile pigments; urobilin and urobilinogen in the duodenal juice demonstrate further the increased hemolytic activity. This hemolytic activity may perhaps be produced by a primary auto-intoxication (Naegeli) or by a hypothetic poison of the intestinal tract (Hunter, Morawitz, Eppinger, Hurst and Bell). Each theory of etiology of hemolytic activity has its followers and its adversaries, and has given rise to many and widely diversed methods of treatments. Limit of space prohibits the discussion of these theories and the relative merits of these therapeutical measures. We incline to accept the gastrointestinal genesis of pernicious anemia and believe that toxins of the intestinal tract pass through the constitutionally changed walls of the intestines. They must be of hemolytic and neurotoxic nature and produce more or less severe damages in the bone marrow or nervous system. It is then easy to understand that according to the prevalence of the toxic action clinical and neurologic pictures are to be found.

Spinal cord lesions were studied in pernicious anemia at first by Noone, who demonstrated such anemic cord lesions in histologic sections. They are formed by small sclerotic lesions beginning around the bloodvessels, producing secondary ascending and descending tract degenerations in the posterior or posterolateral tracts of the white matter. Dana and Putnam in 1891 and Russell, Batten and Collier described a series of cases in which the nervous symptoms of posterolateral tract lesions precede the anemia and state that between Nonne's findings all kinds of different stages occur. They called these pathologic lesions subacute combined degenerations of the cord. Newer investigations of these cord degenerations in pernicious anemia have been made by Henneberg and Wohlwill in Germany and by Williams and Grinker in America. Henneberg called the neurologic picture myelitis funicularis, but later changed this term to myelosis, demonstrating that these primary degenerations are without inflammatory infiltrations in the cord. That such subacute degenerations also involve the gray and white matter of the brain has been shown by Woltman and Troemmer. As already mentioned, the subacute combined degenerations affect only the white matter and more especially the posterior than the lateral tracts, beginning at first in the medial area (Burdach) of the cervical cord and gradually descending below

to the sacral region and ascending into the medulla oblongata and brain. Degenerations have never been observed in the gray matter of the cord or in the extra or intramedullary roots. The histologic picture shows: (1) Granulation and destruction of the myelin sheets of the axis cylinder; (2) neurolytic swelling of the axis cylinder (boules terminales), and (3) secondary tract degeneration.

The degree of the nervous disorder is not always parallel with the severity of the blood disease. If the latter is severe, the course is usually rapid, thus giving no time for the development of changes in the spinal cord and only a few of the focal lesions are to be seen. If on the other hand subacute combined degenerations are numerous, we also find multiple tract degenerations and the blood picture of the preanemic stage. As to the relationship between the development of the blood changes and the onset of neurologic symptoms, there is no constancy whatever. We differentiate our clinical and neurologic pictures as follows: (1) Pernicious anemia without symptoms of involvement of the spinal cord; (2) pernicious anemia with slight signs of spinal cord lesions; (3) pernicious anemia with the typical picture of myelosis. (4) myelosis with the preanemic stage; (5) myelosis without anemia.

The typical neurologic signs are often preceded by subjective complaints, such as weakness, fatigue, numbness, pricking sensation in legs and arms, soreness of tongue, headaches, dizziness, fainting spells, insomnia, depression and delusions, and even hallucinations. Examination reveals the clinical signs: Slightly dilated pupils with sometimes retinal hemorrhages; exaggerated or decreased tendon reflexes, Babinski's sign and cloni; spastic-paretic gait; diminution or loss of the vibratory senses; ataxia and rarely choreoathetotic movements. The sensory findings vary from anesthesia to hyperesthesia or hyperalgesia and are often changeable dependent on the surrounding temperature. Real shooting neurotic pains are often present, and in, at least, 4.9 per cent of cases multiple peripheral neuritis is to be found. The slight muscle atrophy shows quantitative decreased electric irritability. Due to the atrophy of the tongue, the speech is involved and simulates the speech seen in multiple sclerosis. Naturally multiple sclerosis, with its classical picture, makes no difficulty in diagnosis and can easily be eliminated.

As already stated, the blood film does not go hand-in-hand with the clinical findings of spinal cord involvement. Therefore, the diagnosis of myelosis or subacute combined spinal cord lesions without the blood changes of pernicious anemia should be made.

We present histories of cases which in their findings are characteristic for cord lesions, though the blood film would give cause for differences of opinion. These few histories show that in all cases the vibratory sense is disturbed. We wish to call special attention to this neurologic symptom as the earliest objective finding in involvement of the posterior roots. Diminution or loss of the vibra-

tory sense is easily tested for and, if found, cautions us to suspect further development of subacute combined degeneration, even without the blood findings of pernicious anemia.

In regard to treatment, we use blood transfusion, arsenicals and hydrochloric acid with questionable results. In our opinion the therapy of pernicious anemia and of subacute combined degeneration of the nervous system should be taken from a different point of view. There is very probably a relationship between pernicious anemia and hypoadrenia (or Addison's disease), both showing skin pigmentation, adynamia, anemia and similar neurologic findings. We believe that further investigation will reveal the connection between the two clinical pictures.

Case Reports. CASE I.—C. R., an American laborer, aged twenty-nine years, was admitted to the hospital on January 19, 1925, complaining of weakness. He claims that he was in fairly good health until May, 1924, when he began to have soreness of his mouth and tongue and a peculiar taste in his mouth. In July, 1924, he first noted weakness and loss of strength, which gradually progressed until he was no longer able to work. At first, weakness involved only the lower extremities, but later the upper extremities as well became involved. He was transfused three times within a short period of time and after the last transfusion in October, 1924, the patient felt fairly well for about six weeks. In December, 1924, he contracted a severe cold and the old symptoms returned. At this time his legs became numb and the feet, ankles, hands and face became swollen. Several weeks before admission he developed a productive cough, especially in the morning bringing up tenacious purulent sputum in small quantities. The appetite has been exceedingly poor since the onset of the present illness and he has always been constipated. The past medical and family histories are essentially unimportant.

On physical examination it was noted that the patient was well developed but undernourished, with a pasty lemon-yellow color to the skin throughout the body. His speech was slurring in type and at times very difficult to understand. Examination of eyes revealed unequal pupils, the right being larger than left, but both reacting to light and distance. Both bulbar and palpebral conjunctivæ were pale and icteric. The mouth showed marked paleness of the mucous membrane. The tongue was smooth. The neck showed definite visible pulsations and a continuous thrill over the right jugular bulb, which was greatly accentuated with expiration and almost lost on inspiration, and a bilateral systolic bruit. Examination of the chest showed definite infiltration of right apex with coarse leathery friction sounds at the base of right axilla and a fine pleural click at the height of inspiration and the end of expiration at the right scapular spine. The heart showed some enlargement both to the right and left of the sternum, with a systolic murmur heard over entire precordium but best heard in fourth interspace on the left. Abdominal examination showed a palpable spleen and liver. There was marked myedema in the upper extremities, and weakness of both grips, more marked in the right hand. The gait was spastic with muscular rigidity.

The neurologic examination showed normal reactions of all cranial nerves. The biceps and triceps reflexes were reduced and knee jerks absent. The Babinski sign on the left was positive, on the right suggestive. Abdominal reflexes were absent and there was no ankle clonus. The finger-to-nose test showed slight ataxia but no intention tremor or dysmetria. Vibratory sense and sense of motion and position were absent in both upper and lower

extremities. Stereognostic sense was lost. There was no disturbance in sensations, either epicritic or protopathic.

Laboratory examinations: Gastric analysis showed no combined acid; total acidity 30. The test for occult blood was negative. Repeated examinations of stools were negative for ova, parasites and flagellates. The blood Wassermann test was negative and urine examinations were negative. The fragility test showed an initial hemolysis of 0.30 and complete hemolysis of 0.45 per cent sodium chlorid. Blood examination on entrance showed a hemoglobin of 28 per cent, the red cells being 1,330,000 per c.mm. and the differential count normal. Blood smears showed anisocytosis, poikilocytosis and abnormal red cells consisting of megaloblasts, some showing nuclear fragmentation and polychromatophilia.

This case is the typical example of the combined syndrome of a well-developed pernicious anemia and a subacute combined cord degeneration.

CASE II.—J. F., an American hotel manager, aged fifty-eight years, was admitted to the hospital on February 23, 1925, complaining of pricking sensations of hands and feet. He dates the onset of his illness to about April, 1924, at which time he first noted numbness and pricking sensations in the feet. He had no other accompanying symptoms until July, 1924, when he began to have soreness of his tongue and mouth. At the same time he noted swelling of his left leg which persisted for about ten days. After the swelling of the left leg had disappeared, it became weak. Weakness extended to the right leg soon afterward and walking became very difficult, as he could not coördinate nor accurately control his movements. Recently he has also noted weakness of his hands, so that he was unable to hold objects and frequently dropped them. Since the onset of illness, he has had repeated attacks of sore mouth and tongue and has lost about 30 pounds in weight. There was nothing of especial interest either in the past or family history.

Physical examination showed the patient to be well nourished and well developed with a pasty yellow complexion. Eyes showed a definite exophthalmos with an icteric tint to scleræ—otherwise the eyes were normal. The tongue protruded somewhat to the right with slight atrophy of the mucous membrane particularly at the edges. The lungs were essentially normal. The heart showed slight enlargement to the left with definite arrhythmia and pulse deficit. Both the second aortic and pulmonic sounds were weak. No murmurs were present. The abdomen revealed a palpable liver about 5 cm. below the costal margin. The spleen was not palpable.

Neurologic examination: All cranial nerve reactions were normal. On examination of the reflexes, it was noted that the biceps and triceps jerks were reduced; that the abdominal reflexes were absent and that the knee jerks were increased. Bilateral positive Babinski signs were present and the Romberg was + +. The upper extremities showed continuous movements of the fingers, completely choreoathetoid in character. The finger-to-nose test showed definite dysmetria but no intention tremor. There was definite clumsiness in performing the synergy test. The tips in both hands were extremely weak, more marked on the left than in the right hand. The test for sensations showed loss of vibratory sense and sense of motion and position in both upper and lower extremities. Stereognostic sense was lost. Other sensations were preserved. There was marked hyperesthesia in the tips of the fingers and toes.

Laboratory examinations: Gastric analysis showed a total acidity of 10 and absence of free acid. Occult blood was weakly positive. The urine and blood chemistry examinations were essentially negative. Blood and spinal fluid Wassermann tests were negative. A blood-cell fragility test showed an initial hemolysis of 0.47 and a complete hemolysis of 0.30

per cent sodium chlorid. Blood examination showed a hemoglobin of 80 per cent; red cells, 3,525,000; white cells, 8200; and a normal differential count. Smears showed poikilocytosis and anisocytosis. Platelets were reduced.

This case has besides the subacute combined cord signs also symptoms of involvement of the striated body, a very rare observation. The blood film was not fully developed for the diagnosis of pernicious anemia and was more typical of the preanemic stage.

CASE III.—P. C., an American mechanical engineer, aged fifty-seven years, was first admitted on November 2, 1922, complaining of constipation and loss of weight. He dates the onset of his illness to two years before admission at which time he noted marked constipation. He began to lose weight shortly afterward, dropping from about 185 to 152 pounds within a year. In August, 1922, he had the first attack of weakness in his legs, which occurred while dressing. At this time he had unsteadiness associated with vertigo and followed by nausea and vomiting. Ever since the onset of weakness he has had repeated attacks of pricking sensations and numbness in his extremities. His past and family histories were essentially unimportant.

Physical examination revealed a well-developed individual moderately emaciated. His skin was dry and had a yellowish tint and the scleræ had an icteric tint. The tongue was normal. The heart showed a faint systolic murmur, heard best in the fourth interspace on the left side near the sternum. The chest examination was unimportant. The abdomen showed a palpable liver; spleen was not palpable. Neurologic examination at this time was entirely negative.

Laboratory examinations: Gastric analysis showed absence of hydrochloric acid and blood Wassermann test was negative. Urine examinations were essentially negative. Stool examination was negative for blood, ova and parasites. A blood-cell fragility test showed an initial hemolysis of 0.42 and complete hemolysis of 0.32 per cent sodium chlorid. Blood examination on entrance showed: Hemoglobin, 62 per cent; red cells, 1,820,000; white cells, 4600. Differential count was normal. Blood smears showed poikilocytosis and anisocytosis, also showed nucleated red cells consisting largely of megaloblasts, some showing polychromatophilia and nuclear fragmentation.

The blood picture at time of discharge on November 19, 1922, showed: Hemoglobin, 81 per cent; red blood cells, 2,200,000; white cells, 7600.

The patient was readmitted on April 12, 1923, and since discharge he has been improving and gaining in strength. About three weeks before readmission he had several teeth extracted. Since extraction he has again noted weakness of legs accompanied by dizziness. In addition he also developed palpitation and tachycardia.

Physical examination showed a subcyanosis of lips and gums with a decrease in the icterus. The systolic murmur was louder with maximum intensity at the apex and transmitted over the entire precordium both to right and left of sternum.

Blood examination now showed the hemoglobin to be 52 per cent; red cells, 1,590,000; and the white cells 4000.

The patient was transfused three times with whole blood and blood picture at the time of discharge on May 27, 1923, showed a hemoglobin of 78 per cent; red cells, 2,630,000; white cells, 8400.

The patient was readmitted again on March 27, 1924. Since discharge he has felt very good and has been able to work in his office for two and a half months. About two months before his last admission he complained a great deal of dizziness and marked palpitation even on the slightest

exertion. At times he had stiffness of his knees which caused him a great deal of discomfort. For the past six months he developed edema of the ankles and legs.

Physical examination showed at this time a poorly nourished individual with considerable evidence of loss of weight. There was a marked anemic appearance of the conjunctivæ and the mucous membrane of mouth. The tongue had a glossy appearance. Examination of the heart showed a loud blowing systolic murmur at the apex which was transmitted to the right of the sternum. There was marked pulsations of the jugular veins. Reflexes showed knee jerks slightly increased. The Romberg sign was +. There was no disturbance in sense of motion and position. No paresthesias. Vibratory sense was not lost.

On April 13, 1924 he noted some difficulty in walking. Neurologic examination showed loss of sense of position in the toes. Vibratory sense examination gave rise to marked paresthesia. Knee jerks, biceps and triceps were exaggerated.

Blood examination now showed hemoglobin, 40 per cent; red cells, 1,640,000; white cells, 3400.

The patient was transfused again three times with whole blood but the blood picture apparently did not change to any appreciable extent, as at time of discharge on May 17, 1924, it showed a hemoglobin of 46 per cent; red cells, 1,680,000; white blood cells, 4400.

The patient was again admitted on January 20, 1925. Since discharge, weakness and loss of sense of position in the extremities have become more marked. On August, 1924, his legs gave out completely and he was totally confined to bed being unable to walk or use his upper extremities. For past several weeks the flexor muscles of his legs have begun to contract and the knees to bend.

Physical examination now showed an emaciated individual mentally confused. His speech was slow and at times incoherent and hesitating; his memory was very poor. Eye examination showed that the right palpebral fissure and the right pupil were larger than the left. Both pupils, however, reacted to light and distance. The tongue was smooth, glossy and atrophic particularly around the edges of the tongue. The heart did not show any further changes. All extremities showed marked spasticity, more marked in the lower. Flexor muscles of lower extremities showed marked contraction; the thighs being flexed on the abdomen and the legs flexed upon the thighs.

Neurologic examination showed marked increase in knee jerks, biceps and triceps. Bilateral Babinski signs were present. Vibratory sense in both upper and lower extremities was absent. Stereognostic sense was disturbed. There was loss of vesical and sphincter control.

The general course and progress of the patient during stay at hospital was on the decline. No attempt at transfusions or any other form of treatment was made due to his rapid decline. The patient died on April 12, 1925.

This case demonstrates that certain cases of progressive pernicious anemia finally give rise to definite neurologic symptoms which are not demonstrable earlier in the course of the disease.

CASE IV.—E. E., an American housewife, aged sixty-three years, was admitted to the hospital complaining of weakness. She dates the onset of her illness to a period several years before admission, at which time she noted a gradual progression of weakness and fatigue even on the slightest exertion. In the last year before admission she also noticed that she felt dizzy and that she fell rather frequently and was unable to control her feet as she used to. Her past and family history was essentially negative.

Physical examination showed a well-nourished individual. The eye and chest examinations were negative. The heart showed a systolic murmur at the apex which was blowing in character and was transmitted to the third interspace. The liver and right kidney were palpable. The spleen was not palpable.

Neurologic examination showed increased knee jerks, and an abortive patellar clonus on the left with no ankle clonus. There was a marked defensive reaction but no definite Babinski on either side. Vibratory sense in the lower extremities was lost. No ataxia or Romberg signs were present.

Laboratory examinations were essentially negative except that the blood examination showed a typical picture of primary pernicious anemia.

CASE V.—E. G., an American housewife, aged sixty-seven years, was admitted to the hospital on several occasions for observation, study and treatment. She presented a typical and classical picture of primary pernicious anemia on her second admission January 6, 1925.

On physical examination no evidences of any neurologic changes could be elicited. In September, 1924, she noted for the first time, numbness, prickling sensations and marked paresthesias in the distal phalanges, which have progressively become more marked. The first evidence of definite cord changes was noted on March 10, 1925, when she lost her vibratory sense in the lower extremities. No further neurologic change has developed since then.

Conclusion. In our observations, we find that at least 80 per cent of our cases of pernicious anemia presented some form of neurologic manifestation.

It appears that the loss of vibratory sense is almost invariably the earliest sign of neural changes in pernicious anemia and not infrequently a diagnosis of the disease and subsequent development of cord changes were predicted in spite of a normal blood picture.

Cord changes may precede the characteristic blood picture of pernicious anemia, and in such cases the progress of the disease is more rapid, remissions are less frequent and prognosis more serious. Neurologic manifestations are apparently limited to the cord, particularly involving and causing marked tract degeneration of the spinocerebellar and posterior column tracts.

Cerebral involvement are not infrequent, but manifestations are more diversified in type and cannot be localized with the same degree of accuracy as in the spinal cord.

Finally we wish to emphasize that cord findings in pernicious anemia are more commonly present than have been reported, and that the general practitioner should safeguard his observation and interpretation of the neurologic findings, as very often a diagnosis of neuritis, tabes and of other erroneous diseases is made in the early stages of the disease.

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PRESSURE CHANGES IN THE BILIARY TRACT.*

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In the past most of the experimental work on the physiology of of the extrahepatic biliary ducts has been done on anesthetized animals through acute experiments. The anesthetic and various other factors have influenced the results. In order to overcome these objections, and to determine the bile pressures in the intact animal, a method was developed to observe the gall bladder and common duct pressures synchronously by means of a cholecystostomy tube and a T tube in the common duct of the dog. In this work the operative procedures were carried out under anesthesia. The cholecystostomy tube was placed in the gall bladder and the T tube in the common duct near the duodenum. These tubes were allowed to heal in position before observations were made on the intact animal. Thus these pressure readings were not complicated by any external influences or discomfort of the animal. This is an ideal way of studying the pressures in the common duct and gall bladder, as well as the mechanism of the cystic duct and the pressure relationships on either side of it. Besides recording the biliary pressures in several dogs prepared in this manner, a few acute physiologic experiments on the cystic duct of the dog were made, and certain other constant phenomena observed and studied.

* This work was submitted by Dr. Potter to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery, June, 1925.

During the experiments certain pertinent questions with regard to biliary pressure arose which were variously investigated as follows:

1. The determination of the average biliary pressure in the intact dog.
2. The effect of diet on the average biliary pressure.
3. The study of rhythmic pressure waves in the common duct.
4. The confirmation of rhythmic pressure waves in the gall bladder.
5. The relationship of the pressure curve of the common duct to that of the gall bladder.
6. The effect of cholecystectomy on the pressure curves in the common duct.
7. The effect of infection on the pressure curves in the gall bladder and common duct.
8. The study of the sphincter and the pressure relationships at the neck of the gall bladder.
9. The emptying of the gall bladder as studied under the fluoroscope with the use of opaque mediums.

Review of the Literature. The pressure which the sphincter of the common bile duct will maintain has been determined by several observers by means of a manometer attached to a cannula. This was usually placed in the sectioned common duct pointing toward the duodenum, through which when open the pressure at which the sphincter gave way was observed. The results were influenced by the anesthetization of the animals, and possibly also by impairment of the nervous control in the sectioning process (tabulation).

The effect of external stimuli and diet on the biliary pressure maintained by the sphincter has been determined by few observers. Archibald noted that touching the duodenal mucous membrane with hydrochloric acid or pinching it raised the sphincter tone for a few seconds. McWhorter found that magnesium sulphate in the duodenum lowered the sphincter tone from 50 to 100 mm. of water. Jacobson and Gydesen observed the same phenomenon, and also that acids and peptone lowered the sphincter tone. Cole has some evidence that the isolated gastric contents influence the pressure which the common duct sphincter will hold. If one assumes that the biliary flow controls the pressure to a certain extent the following observations have a bearing on the problem.

Martin and Copeman noticed that in the biliary fistula of man there was an increased flow of bile after meals. Auster and Crohn report that bile flows into the duodenum even in the fasting state, while the amount is increased after the ingestion of hydrochloric acid, peptone, bile and fats. Jacobson and Gydesen found an increased flow after certain foods. Rost observed an increased flow after acids. Okada, who experimented with many drugs and foods, noted that starvation decreased the biliary flow, while water, sugar, starch and soda had no effect. The flow was increased by

bread, butter, meat, eggs, acids, peptone, extracts and bile. Rost and Klee and Klüpfel found that in the fasting state bile was discharged into the duodenum at long intervals, whereas peptone and food caused rapid spurts.

Although there are no records of rhythmic pressure waves in the common duct, there are some observations on the subject. Doyon[12] noted contractions of a peristaltic type in the common duct; Westphal observed four contractions a minute of the lower end of the common duct in rabbits and cats, and Copeman, in a case of biliary fistula, noticed that "The act of secretion was found not to consist of a continuous oozing, but short periods of rest followed by a flow in a series of jerks, caused by peristaltic contraction." Harley thought that the "jerks" were mechanical, due to the emptying of the tube. Gerald observed rhythmic contractions in isolated strips of common duct from sheep which responded to certain drugs with a characteristic action. Rost and Klee and Klüpfel record the fact that bile is discharged into the duodenum in spurts. Klee and Klüpfel state that one occurs as each peristaltic wave passes the pylorus.

Rhythmic waves of changing pressure have been observed in the gall bladder during many investigations. Doyon[12] was the first to record them. Okada,[39] using a distended balloon in the gall bladder of the anesthetized dog, found that the rhythmic waves were increased in number when oil, food or hydrochloric acid was injected into the duodenum. Bainbridge and Dale, and Macht have also reported rhythmic pressure waves in the gall bladder. Mann and Giordano noticed waves in animals with fistulæ of the common duct, which could be attributed to the movements of the gall bladder. They found also that in the dog the rhythmic movements ceased when the pressure was more than 340 mm. of water. Freese, by stimulating the proper nerves, determined the contraction pressure of the gall bladder to be about 214 to 313 mm. of Ringer's solution.

With regard to the emptying of the gall bladder, Doyon,[13] in 1894, said that stimulation of the central end of the vagus caused the sphincter of Oddi to relax and the gall bladder to contract. Meltzer,[35] reasoning from his law of reciprocal innervation, thought that this relationship should exist, but there are no records to substantiate it. Furthermore, observers agree that the gall bladder does not contract in the same manner as the urinary bladder.

Eisendrath and Dunlavy, Judd and Mann, Oddi,[36] Rost and many others have observed that following cholecystectomy the stump of the gall bladder and the biliary ducts dilate. Walzel notes that when a rather large stump of the gall bladder is left it dilates to form another gall bladder. Sweet finds that the partial saccules are also dilated. Judd and Mann have observed that if the sphincter of Oddi is cut the ducts do not dilate after cholecys-

tectomy, and if it is not cut at the time of operation the tonicity of the sphincter is lost sometime afterward. In this connection Rost notes that after this operation certain dogs are continent as regards the sphincter of Oddi, while others dribble bile, and peptone does not cause spurts of bile from the papilla of Vater, as in the normal animal. Klee and Klüpfel have confirmed his findings. Rost believes that the determining factor is the length and strength of the sphincter of Oddi. Billard and Cavalié have noted that the flow of bile increases after ligation of the cystic duct. Mann,[27] in 1924, collected all of the experimental and clinical data concerning dilatation of the extrahepatic biliary tract and the tone of the sphincter of Oddi following cholecystectomy.

In studying the pressure relationships in the cystic duct, that is, the pressure necessary to cause a flow through the duct with no pressure in the part studied, Mann found that the cystic duct never maintained a pressure of more than 30 mm.

In trying to study the emptying of the gall bladder under the Roentgen ray Winkelstein ingeniously sewed four silver discs on the serous surface of the gall bladder of the dog. He was unable to discover any change of size before or after feeding. Abramson injected the gall bladder of the dog with neosilvol, but was unable to see it empty under the fluoroscope. Nevertheless, in a dog with a cholecystostomy tube, which was injected with a 150 per cent solution of sodium iodid, he saw opaque material spurt from the gall bladder once during a long period of observations.

Matsuo reports the emptying of the gall bladder following duodenal lavage with magnesium sulphate in accordance with the method of Lyon. Graham's recent test for disease of the gall bladder has shown the slow filling and emptying of the gall bladder by opaque dyes secreted by the liver. It has not shown any marked contraction, although some evidence has been obtained that it does empty. Silverman and Menville observed a decrease in the size of the visualized gall bladder following the duodenal instillation of magnesium sulphate.

One of the most interesting observations on the emptying of the gall bladder was made by Boyden. In a study of the gall bladder in a large series of cats killed after ingesting various foods he noted that the gall bladder was empty after a meal of fat. Whitaker, using sodium tetraiodophenolphthalein as an opaque medium, was able to obtain a beautiful picture of the gall bladder and to show a marked decrease in the size of the shadow after feeding an animal a meal of fat.

Winkelstein and Aschner inserted a cannula into the common bile duct, from which a portion of the hepatic bile had been diverted, and after lavage of the duodenum with magnesium sulphate, obtained dark-colored bile.

Bainbridge and Dale noted that the neck of the gall bladder reacted to epinephrin differently from the rest of the gall bladder.

Methods Used in Experimental Work. *Operative Technique.* In the study of the pressures and the rhythmic pressure waves in the common duct and gall bladder, gentle, quiet dogs were selected and trained to lie perfectly quiet on the left side for long periods. The training period lasted a week or more. At the end of this period the upper abdomen was opened in the median line under ether anesthesia, with the usual sterile precautions. The common duct was isolated and a short longitudinal slit made near the duodenal

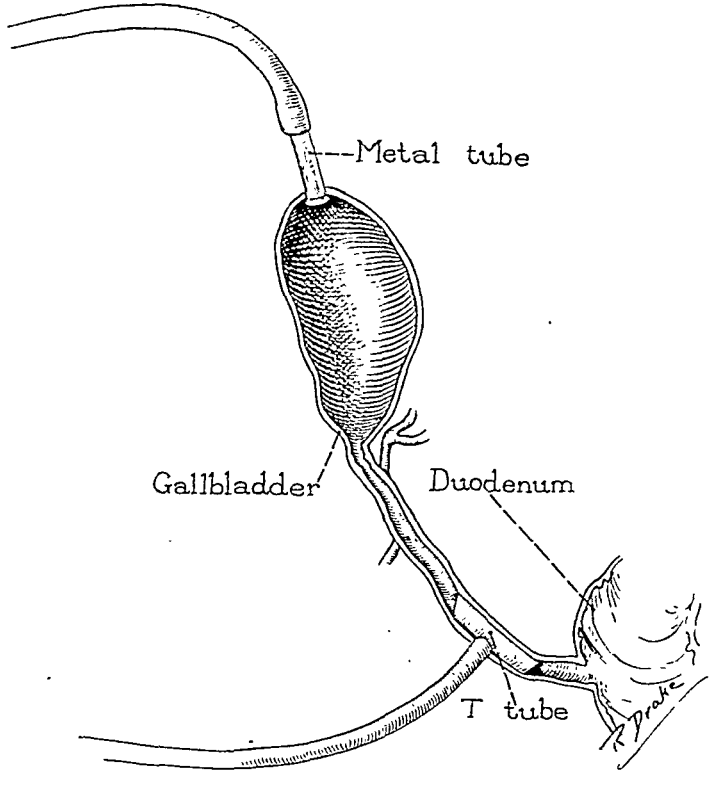


FIG. 1.—Devices by which observations were made in experiments.

end, into which the short ends of a rubber T tube about 4 mm. in diameter were carefully slipped, and the walls approximated with very fine silk sutures to prevent leakage. Care was also taken to avoid injuring the nerves around the duct.

In the dome of the gall bladder a small opening was made, into which was placed a short metal tube with a flange, or a small rubber T tube. These were held in place by means of a purse-string suture. The rubber T tube seemed to be the most satisfactory. Through separate stab wounds in the right rectus muscle the ends

of the tubes were brought to the outside and the incision in the median line closed in the usual manner with catgut and linen (Fig. 1).

In the early experiments the animals were prevented from pulling out the tubes before they became accustomed to them by means of a collar, but as this collar was not wholly effective a different method was devised. The external ends of the tubes after being brought out through the lateral abdominal wall were tucked back under the skin superficially. When the animal became aware of their presence they were brought to the exterior through the original stab wound. When not being used for observations the distal ends of the rubber tubes were tied shut by linen thread so that the usual biliary flow continued down the common duct through the short end of the T tube into the duodenum. Animals prepared in this way ran about normally, with the two tubes healed in position.

Methods of Routine Observation. After a few days, when the abdominal wound had healed and the dogs were again accustomed to lying quietly, the pressure readings were taken by having the animal lie on its left side on a comfortably padded table. The room was kept quiet and the animal allowed to sleep. A little strenuous exercise before the experiment often induced the dog to doze during the observations. When the animal was peacefully settled cannulæ were inserted into the opened ends of the exposed tubes in the lateral abdominal wall. From the cannulæ rubber tubes led to upright glass tubing of 2 mm. inside diameter. These rods were attached to a meter scale whose zero reading was placed at the animal's medium abdominal raphe. The pressure was then recorded in millimeters of the bile which flowed out through the cannulæ into the upright glass tubing attached to the scale. In this paper the bile pressure is considered equivalent to water pressure. When not in use the cannulæ and tubes were kept in an alcoholic solution to prevent infection.

In the first experiments readings of the pressures were taken every ten minutes. The time interval was gradually decreased until the gall bladder and duct pressures were read every half minute. A few records were made of the duct pressure every ten seconds. As it seemed best to take a continuous record an apparatus[40] was developed, the principle of which was to follow the meniscus of the bile by means of a hand-controlled writing point, which recorded the fluid level on a moving drum. These records showed slight variations and could be measured and studied later.

In studying the effect of diet on the pressure the animal after fasting for eighteen hours was fed the test meal. The records were taken from forty-five minutes to one and a half hours later.

In a small series of acute experiments the pressure relations at the neck of the gall bladder in the dog were studied with the animal in the dorsal position. In these the abdomen was opened in the

median line and the viscera packed off with warm gauze and towels. A purse-string suture held a cholecystostomy tube in the gall bladder, while a cannula was placed in the hepatic end of the sectioned common duct. Each tube led to a manometer and the pressure was varied on one side or the other of the neck of the gall bladder and the cystic duct, following which the pressure on the opposite side was noted. At the close of the experiment the dogs were made to rebreathe in an attempt to produce contraction of the gall bladder.

Roentgen ray examinations were made on a dog with a cholecystostomy tube. Through this a barium solution was injected and the animal placed under the fluoroscope first on one side, then on the other.

Results of Experiments. *The Average Biliary Pressure in the Intact Dog.* As the average biliary pressure is varied by diet, and the gall bladder pressure may be greater than the duct pressure, it was thought best to average all the satisfactory duct and gall bladder readings for normal dogs to get the average pressure in the biliary system of the normal intact dog. This was found to be 120 mm. of water. A more important figure is the norm obtained by grouping the records in divisions of 75 mm. of water pressure.

TABLE I.—PRESSURE IN BILIARY SYSTEM OF NORMAL DOG.

Millimeters of water pressure	0–75	75–150	150–225
Number of readings	3	29	5

These figures show that the majority of the readings lie between 75 and 150 mm. of water pressure. This norm, as stated, includes both duct and gall bladder readings, and probably represents quite accurately the actual pressure in the biliary system of the quiet, intact dog.

The average pressure in the gall bladder is greater than that in the duct. In the gall bladder it was 141 mm., whereas in the duct it was 117 mm.

The Effect of Diet on the Average Biliary Pressure. The three procedures used in testing the effect of food on the biliary pressure were fasting, milk diet and dog biscuit diet. Milk caused a constant marked elevation of pressure, fasting gave the lowest pressure, while dog biscuit held a middle position.

TABLE II.—EFFECT OF DIET ON AVERAGE BILIARY PRESSURE.

	Fasting.	Dog biscuit. Pressure in mm.	Milk.
All combined duct and gall bladder readings	93.4	110.8	126.9
In a single dog	95.0	120.0	153.0
Duct	95.0	109.0	130.0
Gall bladder	114.0	129.0	182.0

When the duct and gall bladder pressures are separated the same relationship to diet is found, as would be expected. Furthermore, it is again apparent that the pressure in the gall bladder is greater than that in the common bile duct.

If the experiment is continued long enough after a milk or ordinary diet the pressure gradually drops. The rise of pressure after a milk diet, above the fasting reading, is easily demonstrated by taking a record of the pressure in the fasting dog, feeding the animal milk while on the table and allowing it to sleep an hour. After the nap the record will show a marked elevation of pressure.

The Rhythmic Waves of Pressure in the Common Duct. The common duct curves show three constant rhythmic variations in pressure which probably have a physiologic import. The usual record shows a primary type of wave, which is large and rhythmic, with a gradually ascending up slope and a rather abrupt down slope. The second type of wave is superimposed on the foregoing, is of medium size and occurs about five to seventeen times a minute. Finally there is the third wave which is small, and synchronous with the respiratory movement.

The following records show these rhythmic waves in as many dogs. One is taken with the respiratory recorder to show the relationship of the pressure waves to the respiratory curve. There is also a second marker to show the number of the medium-sized waves each minute (Figs. 2 and 3).



FIG. 2.—Rhythmic pressure curves of common duct.

When the duct pressure is first registered it often shows a distinct "peak" in the early part of the curve as it rises from zero (Fig. 4). In this connection it may be noted that when the intraductal pressure is raised from without it does not drop smoothly and regularly, but in a series of jumps. These may be synchronous with respiration, but we have not definitely determined this point.

The Rhythmic Waves of Pressure in the Gall Bladder. The rhythmic waves of pressure change in the gall bladder have been confirmed, but no observations as to the effect of diet and other stimuli were made. The respiratory waves in the gall bladder were much greater than those in the common duct, due probably to the greater volume of fluid and surface to be pressed on.

The Pressure Relationships in the Gall Bladder and Common Duct Curves. There are two important findings when the common duct and gall bladder curves are studied together: (1) The pressure in the gall bladder may be higher than that in the common bile duct; (2) there is what might be called a "reciprocal pressure change,"

that is, the pressure in the gall bladder rises as that in the duct drops, after which the curves approach each other and meet, to separate again and repeat this relationship (Figs. 4 and 5).

A third constant finding in synchronous records of the gall bladder and common duct pressures is the fact that the pressure in the gall bladder rises more slowly than that in the duct, due probably to the slow filling and distention of the bag.

The "peak" of pressure at the early part of the curve and the gradual fall of pressure after a meal have been described (Fig. 4).

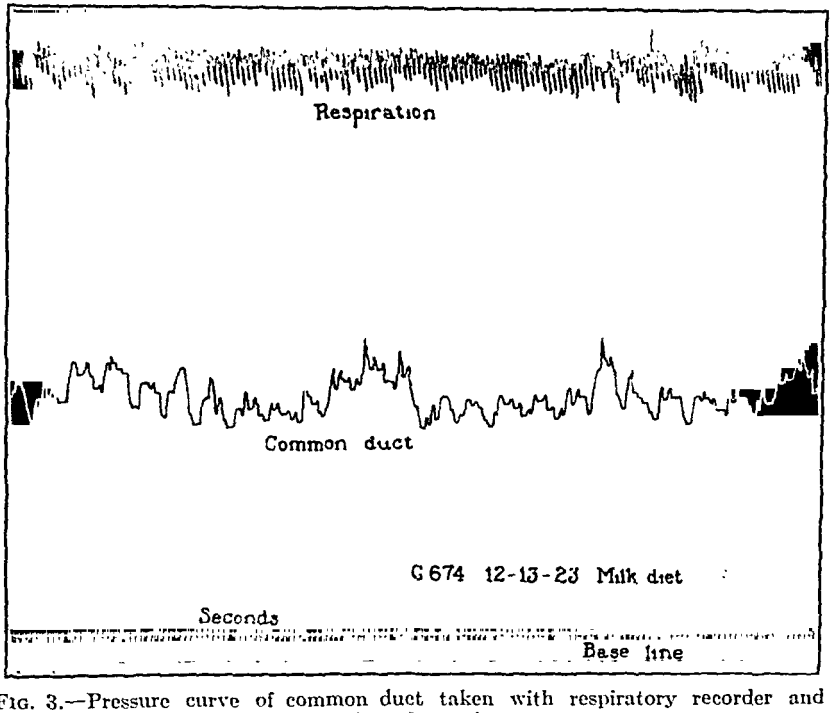


FIG. 3.—Pressure curve of common duct taken with respiratory recorder and second marker at base.

Besides the reciprocal pressure relationship, the slower rising of the gall bladder curve, and the fact that the pressure in the gall bladder may be greater than that in the duct, the curve in Fig. 4 illustrates another phenomenon, probably mechanical, which may be seen after a milk diet when the gall bladder and common duct pressures are recorded together. At the height of the curve the two pressures may separate widely to come together later as the pressure drops. The separation of the curves is probably caused by back pressure from the T tube, due to the fact that at the maximal flow the lumen of the short end of the T tube is not great enough to take the bile away, but backs it up into the gall bladder, raising the pressure. This would seem probable, as the two curves approach each other when the flow and pressure gradually drop

after the milk diet. Furthermore, it is not seen in the curve after the ordinary diet.

Three of the dogs showed the reciprocal pressure relationship in varying degrees. The fact that the gall bladder pressure is at times greater than the duct pressure is a general finding. In the reciprocal relationship the fact that from a common point the duct pressure drops while the gall bladder pressure rises, gives the impression that the phenomenon is physiologic, not mechanical.

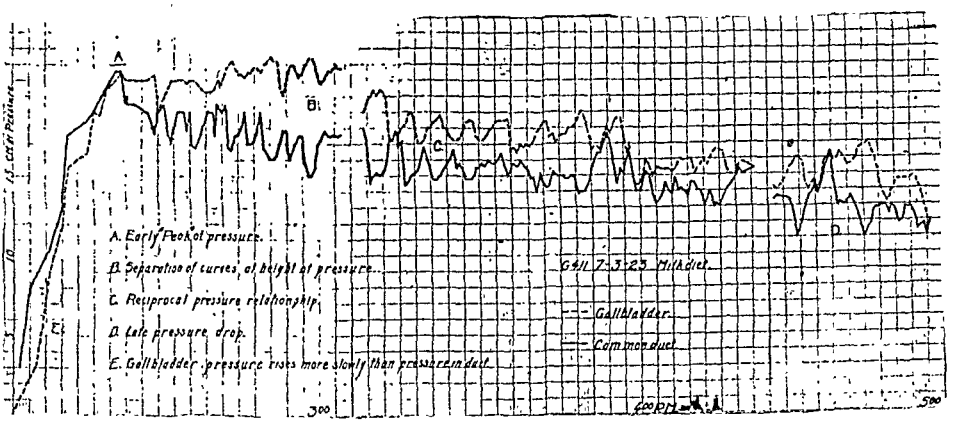


FIG. 4

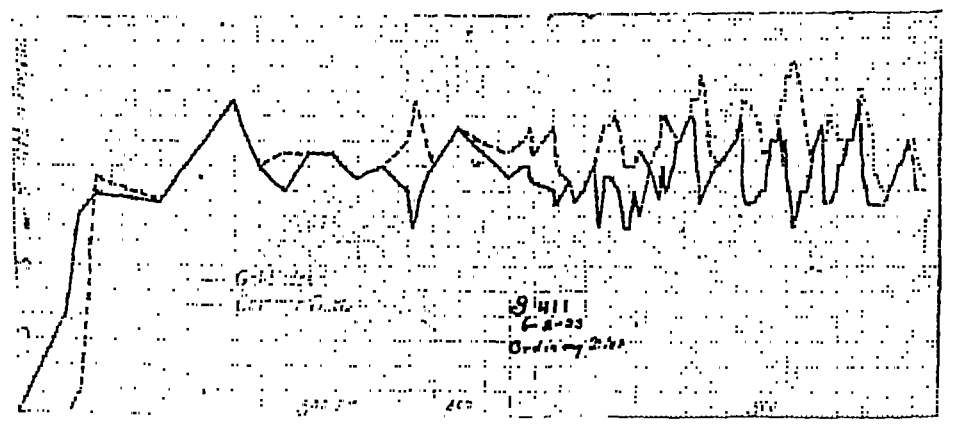


FIG. 5

FIGS. 4 and 5.—Synchronous records of pressures in gall bladder and common duct, illustrating reciprocal pressure change.

The Effect of Cholecystectomy on the Pressure Curves in the Common Duct. A limited number of records were made following cholecystectomy. These show a marked increase in the common duct pressure (235 mm.) and an increase in the amplitude of the large rhythmic waves (Fig. 6).

The Effect of Cholecystitis on the Pressure Curves. The effect of cholecystitis on the waves of pressure in the gall bladder and common duct is to flatten them out, causing a straight line on the

record, and the duct and gall bladder curves run parallel (Fig. 7). The high peaks in Fig. 7 are due to deep sighing respirations.

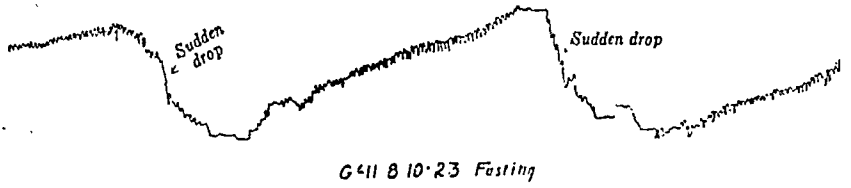


FIG. 6.—Record showing pressure curves of the common duct sixteen days after cholecystectomy.

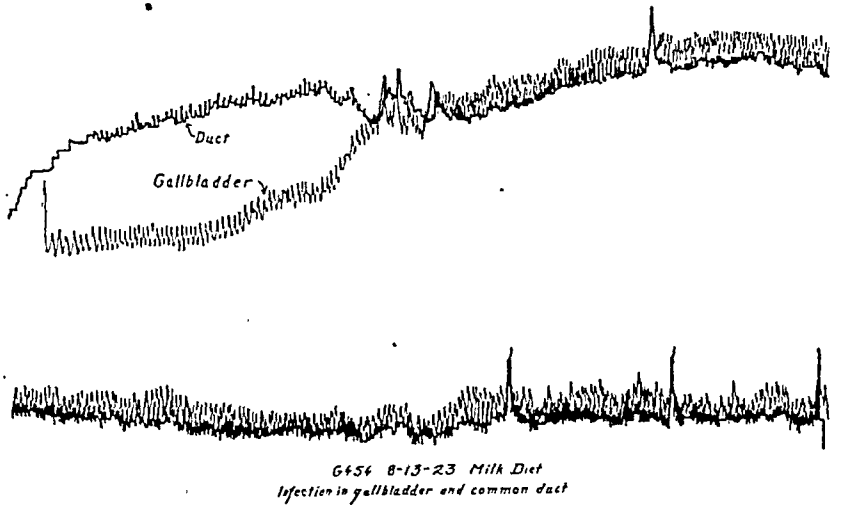


FIG. 7.—Record showing the flattening and the parallelizing of the curves when the gall bladder and common duct are infected.

The Sphincter and the Pressure Relationships at the Neck of the Gall Bladder. The pressure relationships at the neck of the gall bladder were studied in the intact dog and in acute experiments. In the anesthetized animal a low pressure, about 30 to 80 mm. of water, was held from both sides. The pressure which the gall bladder neck and cystic duct could hold was decreased by raising the pressure several times to a high point on either side. After a short rest the pressure maintained would return to the original reading. Apparently the high pressure ironed out the mechanism for a short time.

The rebreathing of the dogs did not cause contraction of the gall bladder.

One intact animal in excellent condition was able to hold 150 mm. of water pressure from both sides by means of the resistance mechanism at the neck of the gall bladder.

The Emptying of the Gall Bladder as Studied under the Fluoroscope by the Use of Opaque Mediums. One dog was examined under the fluoroscope. Through a cholecystostomy tube the gall bladder was filled with a small amount of barium solution and the animal studied, lying first on one side, then on the other. The gall bladder appeared to undergo a movement which may have been peristaltic or "squashing," due to rhythmic constriction. From the neck of the gall bladder spurts of opaque material were projected at intervals, apparently rhythmically.

Discussion. The average sphincter pressure as found in the normal intact animal closely parallels the pressure readings of the more recent observations during acute experiments, and is much lower than the readings of earlier investigators.

If the bile pressure is determined by the bile flow to any extent the effect of various diets could be anticipated somewhat.[2, 3, 8, 10, 19, 21, 22, 35, 38] Fasting might be expected to produce the lowest pressure, whereas milk and the mixed diet found in dog biscuit would cause a greater pressure. Furthermore, the fact that bile is needed in the assimilation of the fats in the milk would make it seem reasonable that the pressure would be greater with a milk diet than with a diet of dog biscuit, although according to Boyden's work a pure fat diet might cause the reverse.

The large waves in the common duct are, we think, unquestionably due to the mechanism of Oddi's sphincter on the flow of bile. This idea is supported by the slow rise and rapid drop of the wave, which would be expected from a gradually increasing pressure relieved by the opening of the sphincter of Oddi. Rost, and Klee and Klüpfel have shown that bile is discharged at intervals in spurts into the duodenum. In addition, the increase in the amplitude of the waves following cholecystectomy gives the impression that they are an intraductal rather than an extraductal event. Pressure from the adjacent duodenum must also be borne in mind as a possible source of the large waves. The medium waves may be due to: Contraction in, and pressure from, adjacent organs, peristalsis in the duct itself, or to some contraction in the gall bladder. This last is apparently ruled out by their presence when the gall bladder is not functioning for any reason, and after cholecystectomy. The most likely adjacent organ to cause a disturbance in the pressure reading of the duct is the duodenum. It was not possible to determine any relationship to any pressure waves in the common bile duct to those in the duodenum, that is, peristalsis of the duodenum. Furthermore, the waves in the duodenum, do not bear any resemblance to the curves of the common duct which have been shown. The effect of respiration on the pressure curves can practically be ruled out with the exception of sneezing, coughing and straining movements, which cause marked changes in abdominal pressure. The ordinary respiratory effect on the pressure

is a small superimposed wave which is greater in the gall bladder curve than in the common duct, due probably to the greater surface and volume of the gall bladder. The fluctuations due to breathing can easily be checked and shown to be synchronous with a respiratory record. The peak in the curve at the start of the record is apparently due to a resting of the sphincter mechanism by the sudden release of pressure when the bile flows into the tubing. As the pressure mounts it goes for a moment above the average pressure before the sphincter mechanism is "touched off" into its usual action. The dropping of the duct pressure by jumps would also seem to indicate that the intraductal pressure had a share in controlling the sphincter, that is, the high pressure causes the sphincter to open allowing the pressure to drop. Following this the sphincter closes, checking the drop, but, the pressure still being too high, the sphincter again opens. This phenomenon of dropping by jumps may have some relationship to respiration, but this point has not been determined. The fall in pressure after a meal certainly suggests that the bile flow affects the pressure.

It is barely possible that there are two types of pressure waves in the gall bladder: One caused by a squashing action and another by a contraction of a peristaltic nature. The fluoroscopic examination cautions us to leave this question open, however.

The most significant observation brought out in this work is the "reciprocal pressure" relationship in the curves of the gall bladder and common duct. While more records are necessary, there is no question but that the ones shown are suggestive. If the drop of pressure in the duct is interpreted as the opening of Oddi's sphincter, and the rise of pressure in the gall bladder as the contraction of its musculature, Meltzer's law of reciprocal innervation is exhibited as applied to the sphincter of Oddi and the musculature of the gall bladder. However, it is apparent that the gall bladder does not contract completely.

The flattening of the curves in cholecystitis with the tract acting as a conduit may be of practical importance. Bollman, Mann and Depage have shown that there is little concentration in the inflamed gall bladder. These two observations would tend to show that dyes excreted by the liver as opaque mediums for Roentgen ray examinations, or as bactericidal agents in inflammatory conditions of the biliary tract do not move slowly enough or become sufficiently concentrated to be effective at these times. The breaking down of the contraction mechanism in itself may be an important factor in preventing concentration.

The rise in the duct pressure and the amplitude of the sphincteric waves following cholecystectomy might be anticipated from the observations of others on the extrahepatic dilatation of the biliary ducts following cholecystectomy. This certainly suggests a "pressure" dome effect. The latter may be one of the mechanisms for

furthering the absorption of substances from, and concentration of, bile in the gall bladder.

The fact that the neck of the gall bladder is capable of maintaining pressure from either side is another interesting observation, previously recorded by Mann, whose pressures were not quite so high. The exact physiologic relationship and importance of this fact have not been determined.

The fluoroscopic observations of the emptying of the gall bladder in rhythmic spurts are not conclusive. However, with the foregoing data it is very suggestive that there is a sphincterlike mechanism at the neck of the gall bladder. The spurts may have been due to barium particles sticking in the cystic duct. In further work a solution of sodium iodid should be used to overcome this objection.

In view of the curves previously shown, it would seem that during the contraction of the sphincter of Oddi the bile is forced into the gall bladder. That most, if not all, bile enters the gall bladder is shown by the appearance of excreted dye almost simultaneously in the duct and gall bladder. Here it is concentrated, and when Oddi's sphincter relaxes a variable amount of gall bladder contents is forced out, perhaps none at times, but with the next closing more bile is forced into the gall bladder. At the same time that the bile is being concentrated it may be that substances useful to the organism are being extracted from the bile. The "pressure dome" effect of the gall bladder is probably a mechanism helpful in concentration. During the fasting period, with long intervals between relaxations, there is ample opportunity for considerable concentration. It is possible that the sphincteric control at the neck of the gall bladder may play a part during these fasting periods. With the ingestion of food and the outflow of bile this more concentrated bile by a gradual pumping action is slowly washed out, to work more perfectly in assimilation. That all is not washed out is seen by the retention of dye sometimes for nearly a week. This outflow may be a most important item in controlling the secretion of bile, as pointed out by Mann.[29]

Summary. The average sphincter pressure in the intact dog is 120 mm. of water. The pressure varies according to the diet. Of the diets studied, fasting gives the lowest pressure and milk the highest.

In the pressure curves for the common duct, besides the small respiratory waves, there are large waves, probably of sphincteric (Oddi) origin, and medium waves, possibly due to peristalsis in the musculature of the common duct. The rhythmic waves of pressure change in the gall bladder have been confirmed.

The pressure in the gall bladder is greater at certain periods than that in the common duct. There also appears to be a reciprocal pressure relationship in the gall bladder and common duct.

Infections in the biliary apparatus cause a flattening of all curves

and a destruction of the contraction mechanism, as shown by pressure variations. Cholecystectomy caused an increase in the common duct pressure and in one case an increase in the amplitude of the sphincteric waves.

There is a sphincter-like mechanism at the neck of the gall bladder capable of maintaining a slight pressure from both sides.

In one instance fluoroscopic examination showed barium being discharged in rhythmic spurts from the gall bladder.

TABLE III.—PRESSURES MAINTAINED BY THE SPHINCTER OF THE COMMON BILE DUCT.

Observers.	Animals.	Pressure, mm.
Oddi[37]	Dog	625
Archibald	Dog	180–330
Judd and Mann	Dog	100–150*
Mann[26]	Dog, cat, goat, rabbit, guinea pig	75–100
	Rat, gopher	30
Jacobson and Gydesen	Dog	150
McWhorter	Dog	100–200
Cole	Dog	150
Winkelstein and Aschner	Dog	60–65

* This was reduced to less than 40 mm. by excision of the gallbladder.

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SUBSTERNAL THYROID.*

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SUBSTERNAL thyroid has been variously designated as intrathoracic, retrosternal, mediastinal goiter or struma profunda. This condition was first described as an anatomic finding by Haller[1] in 1749. From the clinical aspect substernal thyroid has apparently been neglected, as witnessed by the paucity of reports in the literature, although as early as 1830 Lingl[2] described the clinical picture. However, anatomists and surgeons have, from time to time, drawn attention to the occurrence of goiters within the chest. From our personal experience and that gleaned from an analysis of the literature, it is not as rare as it is usually thought to be. This apparent rarity may be explained by the fact that the presence of such condition may readily be overlooked; for a substernal thyroid may be symptomless and when producing recognizable features, is frequently mistaken for other conditions that may occur within the thorax.

Because of these facts and because of the inoperability of many cases, this condition has been chiefly of interest from the pathological, anatomical and occasionally from the surgical standpoints. It is therefore the purpose of this paper to draw attention especially to the symptoms and physical findings of this type of mediastinal tumor.

Clinically, substernal thyroids are of two kinds, either a retrosternally placed parent thyroid or an intrathoracically placed aberrant thyroid. Aberrant thyroids are classified as false aberrant thyroids, or glandular masses that are attached to the main thyroid either by fibrous or other tissues, and true aberrant thyroids, or glandular masses that have no connection with any other thyroid tissue that may be present.[3,4] The latter are the results of congenital *anlagen*.

The terms substernal, intrathoracic, aberrant and retrosternal thyroids are very loosely employed in the literature, especially by surgeons, who are prone to call a lobe that has slipped slightly behind the manubrium a retrosternal thyroid. The terms false and true aberrant thyroids are also very misleading. A mass of thyroid is either aberrant or not. It would therefore clarify the subject to limit the terms as follows:

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1. Substernal, to abnormal descent of the main gland, a lobe or an adenoma.

2. Intrathoracic goiter, to aberrant glands growing within the chest.

A brief consideration of the etiologic factors concerned in the production of these tumors is apropos. Thyroptosis or the descent of a normally placed thyroid is responsible for the misplacement of an entire gland, or either lobe of the gland. Especially is this true of the hyperplastic and enlarged types of glands. The dragging influence, the consequence of respiratory efforts, the dragging effects of a tumor growing within the substance of a normally situated thyroid, the effects of tight collars, and training by manipulation for cosmetic purposes, and even gravity itself, are all pathogenic influences in the causation of retrosternal goiters. Because of these latter mentioned factors this condition is therefore more frequently seen in older than in younger individuals.

Aberrant thyroids have been found in various situations from the base of the tongue to the pericardium and lungs. It is for this reason that experimental myxedema is difficult to produce in animals, especially in dogs. Schwartz and Thompson[5] found in 30 dogs, successively examined, that in 24 there had been thyroid rests about the arch of the aorta. His at one time believed that the lateral lobes of the thyroid gland developed in the fourth branchial cleft. Should this be the case, although still a matter of dispute amongst embryologists, it would give an embryologic basis for the occurrence of such accessory or aberrant thyroids discussed in this paper; namely, the substernal variety. On the other hand, the thymus gland develops from the third branchial cleft and descends to a position behind the sternum. It is therefore conceivable that in its descent into the thorax, it may drag part or the entire thyroid into the mediastinum. Furthermore, the close proximity of the points of origin of the thyroid to the arch and ascending portion of the aorta in fetal life, and the subsequent migration of the heart into the chest, may drag thyroid rests into the chest. These *anlagen* may subsequently take on either a hyperplastic or other pathologic changes similar to those induced in the normally situated thyroid gland. Various influences, such as endemic conditions, menstruation, puberty, menopause and pregnancy may affect the aberrant gland in the same manner as the normally situated gland.

Substernal thyroid may be fixed or mobile. Violent respiratory efforts may force a goiter already within the chest into the neck or *vice versa*, thus giving rise to a condition known as "spring goiter," "goiter mobile," or "wandering goiter." On the other hand, it is more usual, owing to its size or to adhesions, that the goiter remains fixed within the chest, so that escape through the upper outlet of the thoracic cavity is impossible.

The size of aberrant glands may vary from that of a tiny nodule to a structure several times larger than the normal thyroid itself, the size and shape of the mass depending on the yielding property of the surrounding tissues during the development of the gland and to the rapidity of growth. These rudimentary glands, as has been stated, have been found anywhere from the base of the tongue to the root of the aorta, within the pericardium and the pleura. In the latter it may reach such size as to cause severe symptoms of lung compression and even prevent the normal lung expansion.

These glands may supplement or take the function of the normal gland itself. Therefore, they are subject to the same pathologic changes in about the same proportion as is common to the normally situated thyroid, viz; a parenchymatous enlargement with colloid involution being most frequent. An unusual, though interesting, form is the development of large cysts due to the breaking down of an adenoma.[6,7] Malignant changes are also common.

Incidence. From 1912 to 1920, Czermack studied all the goiter material occurring in the Innsbrucker Clinic, and out of 1473 goiters present, 487, or 32 per cent, were retrosternally situated. Of these 487 retrosternally placed goiters, the right lobe was retrosternal in 251 cases, or 51 per cent. The left lobe in 148 instances, or 31 per cent, and the isthmus 29 times, or 6 per cent. The left and right lobes together, he found 59 times, or 12 per cent. Reimach found 31 substernal out of 162 cases of goiter. Class found 10 out of 106; Kocher found it in 10 per cent of his cases. Monnier[8] out of 670 cases of goiter found 117 to be substernal, 17 deeply intrathoracic From January 1, 1917, to June 6, 1920, 4006 thyroidectomies were performed in the Mayo Clinic[9] for simple colloid and adenomatous goiters. Of these 542, or 13.5 per cent, were found to be partially substernal, and 25 per cent of these classified as intrathoracic.

In a series of 495 teleoroentgenograms taken in conjunction with the routine cardiovascular examination, we found 6 cases of substernal thyroid. There is no doubt that where a greater and more varied series of Roentgen ray examinations of the chest is made, the incidence is greater than that which has been reported in the literature. It seems from our experience that the roentgenologists are unaware of this fact, for they invariably diagnose such cases of substernal thyroid as aneurysm of the aorta.

In our review of the literature, we have found that about 80 per cent of retrosternal thyroids occur in women; and that the age is most common between fifteen and thirty-five years. One can readily conceive from the above the frequency of struma profunda; for about 7 to 10 per cent of all cases of goiter fall into this category.

Diagnosis. The diagnosis of this condition is only possible by an accurate analysis of all the symptoms presented. These may

be grouped under two distinct headings: (*a*) Remote or toxic symptoms induced by hyperactivity of the gland or hyperthyroidism. (*b*) Pressure symptoms resulting from mediastinal involvement and its adjacent structures.

The toxic effects of this anomaly may vary from that of a mild thyroid hyperactivity to that of marked hyperthyroidism, with symptoms of a fully established Graves disease, yet without visible thyroid enlargement of the neck. Frequently, obscure cases, presenting only an auricular fibrillation of unknown origin in a heart, apparently not diseased, is due to a small goiter that has had a tendency to extend down behind the sternoclavicular joint or to an aberrant intrathoracic thyroid. All such cases of auricular fibrillation, the type often designated as idiopathic, in the absence of the usual etiologic factors, should be carefully investigated as to the absence or presence of a substernal thyroid. Any patient who presents himself or herself with symptoms suggesting an overactivity of the thyroid, (rapid pulse, nervousness, irritability, debility, and so forth), plus any sign or signs of intrathoracic pressure, should receive the benefit of fluoroscopic and Roentgen ray investigations to determine the presence of an intrathoracic goiter.

The symptoms caused by compression of the various structures within the thorax are too well known to necessitate recapitulation. However, of special interest are those cases simulating asthma, chronic emphysema, aneurysm of the aorta, mediastinal and intrathoracic malignancy, etc.

The fixation of the trachea by an intrathoracic goiter may inhibit the normal excursion of the larynx; an important diagnostic factor. By placing the finger deeply in the suprasternal notch, one feels a mass which has the consistency characteristic of a goiter: firm elastic and finely lobulated, and at the same time rising with the larynx during coughing and swallowing. In contradistinction to an aneurysm there is no palpable pulsation of an expansile character. Oliver's sign (tracheal tug) is never present in substernal thyroid. Wuhrmann[10] claimed that a high degree of tracheal stenosis, a deeply placed larynx and the absence of palpable thyroid in the normal situation, should suffice to render a diagnosis of retrosternal struma.

Certain muscular movements, such as sudden exertion or flexion of the head, may cause the mass to become wedged in the upper thoracic inlet. This results in spells of obstructive breathing, coughing and a choking sensation. Such intermittency is not produced by any of the other varieties of mediastinal growths, except esophageal diverticula. When the latter is present, the shadow found on Roentgen ray examination is not constant. This can be clearly differentiated from substernal thyroid by careful barium studies. Signs and symptoms of mediastinal compression associated with a visible adenoma of either lobe of the thyroid should render a

diagnosis of intrathoracic goiter. Large intrathoracic goiters may remain symptomless owing to the capaciousness of the thoracic cavity, the relative mobility of its contents and the faculty of its contents to be readily displaced, yet not actually being compressed. The latter, however, is not true of the recurrent laryngeal nerve, for displacement of the large arterial trunks usually exerts traction, thereby causing a total or partial paralysis.[11] The pressure effect upon the recurrent laryngeal nerve is slow in onset, and the cords accommodate themselves, so that a laryngoscopic examination is essential to detect the paresis. Hoarseness was present in 10 per cent of the cases. Pain is never present unless the tumor is malignant, but a sense of fulness in the upper chest is a very frequent symptom.

Percussion as an aid to diagnosis is at best unreliable; definite, positive findings being ascertained by means of the fluoroscope, Roentgen ray and bronchoscope. Hunermann does not advocate the use of bronchoscopy, owing to the danger entailed, and claims that it seldom gives one an idea of the position, size and type of tumor dealt with. Even with the Roentgen ray errors are possible, but only as regards the type or pathology of the mass present. An intelligent and complete examination, including the fluoroscope and Roentgen ray of all patients presenting symptoms of socalled "idiopathic" auricular fibrillation, severe asthma, persistent cough, and aneurysm would prevent such diagnosis being made.

Roentgan ray examination frequently reveals the trachea to be compressed and deviated from the normal. At times the Roentgen ray findings are confusing. It is usual to mistake an intrathoracic goiter for a sacculated aneurysm of the ascending arch of the aorta which it may simulate very closely. Fluoroscopy is a great help in differentiating between the two. If the shadow noted moves synchronously with the respiratory movements and should it definitely lack expansile characteristics, the diagnosis of aneurysm is immediately eliminated. Occasionally an aneurysm may lack this characteristic because of firm clots within it. In such cases Roentgen ray plates when carefully examined may show a distinct line of demarkation between the shadow and the aorta. An oft confusing shadow is that of a persistent thymus. The latter is infrequently seen in adults; it is as a rule bilateral, and has a more hazy and indistinct outline than other thoracic growths. It does not attain the size of an intrathoracic goiter, and rarely, except in infants, gives rise to severe signs and symptoms of compression.

Hodgkin's disease and lymphosarcoma should seldom cause difficulties in the differential diagnosis. They are situated at the lung hilus and spread peripherally in a butterfly fashion. They seldom have as distinct a margin as intrathoracic goiters, are usually bilateral and frequently infiltrate the adjacent tissues. The progress of the latter diseases are more rapid and always downward,

Finally, all tumor masses in the upper mediastinum in close proximity to the aorta should always arouse suspicion of retrosternal struma, expecially if on Roentgen ray examination the shadows have a sharp, distinct and roundish outline, and do not pulsate when viewed under the fluoroscope.

Case Reports. CASE I.—R. H., female, aged fifty-five years, Russian, was admitted to the Montefiore Hospital, with the following complaints: inability to walk, irritability, anxiety, insomnia, headaches and fainting spells. She also complained of dyspnea on exertion. Her family and past history are irrelevant. The patient presented the following positive findings: Her face was flushed. There was a moderate exophthalmos plus von Graeff's sign. The thyroid gland was enlarged, especially to the left. The superficial cervical veins and those over the sternum were enlarged, tortuous and engorged. The heart was moderately enlarged to the left. The sounds were feeble but no murmurs were audible. There was a wide area of dulness beyond the manubrium sterni on either side, with tubular breath sounds over the right upper lobe. The diagnosis was that of hyperthyroidism, aneurysm of the aorta or mediastinal tumor. The roentgenologist's report was that of aneurysm of the arch of the aorta. Exactly one year later the Roentgen ray findings remained the same. No fluoroscopic examination had ever been made. The patient died and autopsy revealed the following: Advanced generalized arteriosclerosis, hypertrophy of the left ventricle, large adenoma of the thyroid extending into the upper anterior mediastinum with compression of the surrounding structures. There was also degeneration of the caudate and lenticular nucleus, and a small adenoma of the adrenal.

Cross section of the thyroid showed a structure of average consistency situated between the two lobes as an isthmus composed of a large globular mass, 5 by $3\frac{1}{2}$ by $2\frac{3}{4}$ cm. in size. The consistency of this mass was greater than that of the thyroid, and in some portions it was calcified to a stony hardness. On cross section this isthmus had an irregular architecture, in some places a translucent fleshy appearance. There were small hemorrhages here and there, with islands of colloid. The appearance was that of a fetal adenoma, showing areas of degeneration and calcification. In addition to this globular mass, there were two other globular masses, one situated on the right side $6\frac{1}{2}$ by 5 by $\frac{3}{4}$ cm., and on the left side, a mass 8 by 6 by $4\frac{1}{2}$ cm. On section these masses were similar to the mass of the isthmus, and like it were enclosed in a thin fibrous capsule. These two masses were attached to the isthmus and to the right and left lobes of the thyroid respectively by fibrous strands adherent to the capsule.

Before removal from the body these masses occupied the same position in the thorax, corresponding to the two previous Roentgen ray shadows.

Sections from various portions showed microscopically, a picture of fetal adenoma with atrophy and replacement fibrosis.

CASE II.—S. O'M., male, aged thirty-eight years, was born in Ireland. He complained of fatigue and frequent attacks of palpitation and "nervousness." His family and past personal history were negative. His present illness dated back about a year. Recently, he gradually lost weight, and with this there were some precordial pains, with a sensation of fulness in the upper mediastinum. This fullness was slight. At times it would increase and induce spasms of coughing. Aside from the above his entire personal history was negative. Physical examination revealed the following positive findings: The patient was a lean enteroptotic individual. There was an overactive heart, slight tremors of the hands, and a generalized hyper-reflexia. Otherwise, physical examination was entirely normal. Fluoroscopic examination presented a shadow lying to the right of the ascending arch of the aorta. It was the size of a lemon and moved with each pulsation of the aorta, but distinctly lacked the expansile character to its movement. The movement was merely due to the transmission of the aortic pulsation. Its outline was sharp and distinctly circular and contained many calcified masses within its body. There also appeared to be discreet calcified masses ascending toward the neck. A teleoroentgenogram showed that the mass was distinct from that of the aorta which it fairly straddled. The heart was of the dropped type and rather small. The electrocardiogram, except for a left ventricular preponderance, showed normal deflections.

CASE III.—J. S., aged fifty years, Russian, female, complained of shortness of breath and palpitation. The history of the present illness began two years ago with palpitation and dyspnea on exertion. Her past personal history was otherwise normal. The physical findings were entirely negative except for slight increase in cardiac dullness to the left and an irregularity in the rhythmicity of the heart sounds (auricular fibrillation). Roentgen ray revealed a shadow apparently arising from the arch of the aorta. This was previously diagnosed as an aneurysm. The heart was enlarged to the left but the aorta was normal. Fluoroscopic examination showed that the shadow lacked expansile pulsation and was distinct from the shadow of the aorta, as evidenced by the Roentgen ray photograph. The electrocardiogram revealed a typical picture of auricular fibrillation with occasional extrasystoles, probably arising in the right ventricle.

The two latter cases were previously examined by Roentgen ray, and diagnosed as aneurysm, owing to the masses observed within the chest. Careful fluoroscopic examination, and good Roentgen ray plates would have avoided such mistakes. In the



FIG. 1.—Case I. Roentgenogram of chest showing the large intrathoracic shadow. The denser structure of arch of aorta is distinct.



FIG. 2.—Case I. Specimen of thyroid adenomata removed at autopsy, showing the close proximity to the aorta.

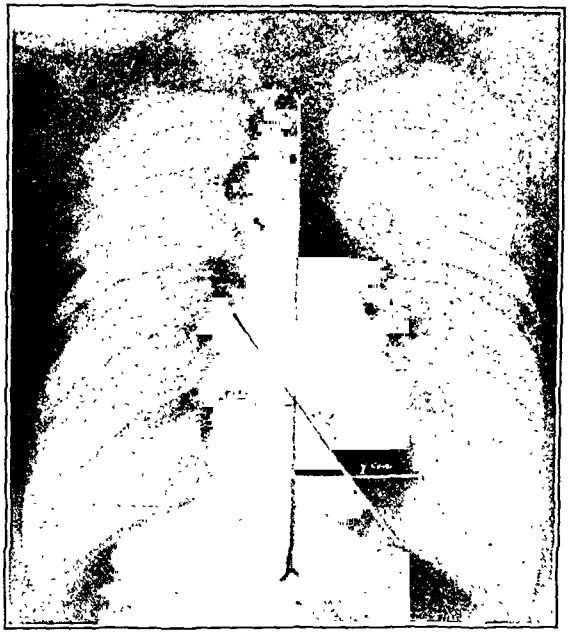


FIG. 3.—Case II. Teleroentgenogram. The shadow to the right of the aorta resembles a sacculated aneurysm for which it was mistaken. It is an example of an aberrant intrathoracic goiter with areas of calcification.



FIG. 4



FIG. 5

FIGS. 4 and 5.—Cases III and IV. Teleroentgenograms. The shadows are alike and are situated behind the right clavicular sternal region. This is a very common sight for retrosternal goiters.



FIG. 6.—CASE VI.—Teleroentgenogram. A large retrosternal mass gave rise to marked symptoms and signs of mediastinal compression.

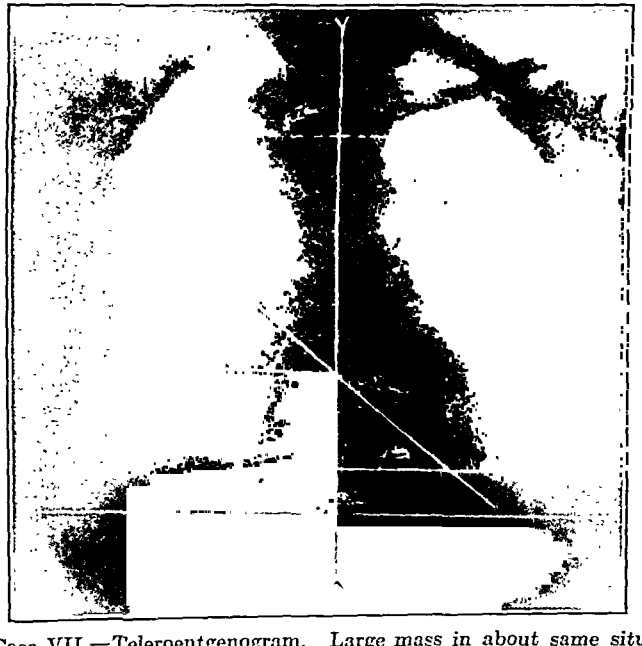


FIG. 7.—Case VII.—Teleroentgenogram. *Large mass in about same situation as* Case II, and giving rise to no symptoms.

former an expansile pulsation should be sought for in order to render a diagnosis of aneurysm, and in the latter, a mass distinct from that of the aorta should be detected so as to eliminate a diagnosis of the same. Case II, presenting an auricular fibrillation, was given quinidin with no effect, apparently due to the fact that the thyroid was the agent in its causation. The patient has been seen a number of times after taking minute doses of thyroid and has improved remarkably.

CASE IV.—M. L., male, aged forty-one years, Austrian, auctioneer, complained of pains in the precordium for one year. This began with a "nervous breakdown" following business worries. Pain was exaggerated by eating and exertion and lasted for an hour or more. There was no dyspnea or other cardiopulmonary symptom. The entire physical examination was negative except for a generalized hyper-reflexia. Fluoroscopic examination revealed a small well-defined shadow below the right sternoclavicular junction which moved with respiration. It was about the size of a small lemon. Its character, size and position were well shown by the teleroentgenogram. Iodin in minute doses given intermittently resulted in complete recession of all his subjective symptoms.

CASE V.—E. R., male, German, manufacturer, aged fifty-one years, complained of pain of an anginoid character, with typical radiation. There was pain in the precordium for the past six months following eating and exertion. His father died of angina pectoris, otherwise his family and personal histories were negative. Physically, he presented a systolic murmur over the apex. There was a trace of sugar in the urine. The Roentgen ray picture was identical with that of case IV (M. L.). The electrocardiogram showed evidence of a left ventricular preponderance.

CASE VI.—R. de S., aged forty years, female, Italian, complained of shortness of breath, with swelling of hands and face. Her family and past histories were negative. Her present illness began a year and a half ago. Her hands and the veins of the upper extremities became visibly swollen. Palpitation became severe in the last three weeks. Dyspnea was very distressing on the least exertion. Examination revealed a large distended mass of veins in the neck and both upper extremities, with some cyanosis of both hands. On placing finger in episternal notch a firm elastic mass was felt. There was a distinct increase of dulness on percussion over the manubrium sterni, and a rough systolic murmur was audible over the mitral area, but the heart was not found to be enlarged. The patient was three and a half months pregnant. The urine showed a heavy trace of albumin, but no casts or erythrocytes were present. A teleroentgenogram revealed a large mass behind the

manubrium reaching further toward the left than the right. It was distinct from the shadow of the aorta and was pulseless under fluoroscopic view. The heart was slightly enlarged and the aorta somewhat dilated.

This patient was originally sent as a case of mediastinal new growth. However, this was apparently a retrosternal thyroid, which, under the stress of pregnancy, had undergone hyperplastic change. Thyroid was given in a dose of 0.0065 gm. (gr. $\frac{1}{10}$) three times a day. The improvement in signs and symptoms was remarkable, and she was able to give birth to her child at term without difficulty. In a recent communication with her physician it was learned that she had been delivered successfully of another child.*

CASE VII.—B. S., a female, aged forty-six years, was born in Germany. Her condition was accidently discovered while undergoing a gastro-intestinal examination. There was a shadow seen, the size of a large orange behind the upper portion of the sternum, more to the right than to the left. It extended into the neck and could be manually felt as a distinctly nodular, elastic, firm mass. The heart and aorta were somewhat enlarged. This patient has been frequently observed since the original examination and is in good health. The mass has not enlarged and no treatment has been instituted. She came from a region where goiters are prevalent, and her mother also, has a large goiter.

This is an instance of a large thyroid mass situated in the upper mediastinum, giving rise to no signs of compression in spite of its location and diameters.

Treatment. Very little can be said about the treatment as many of these cases are symptomless and may remain benign for many years. In 2 of our cases, minute doses of thyroid seemingly caused recession and great symptomatic improvement. The small doses of iodides as advocated by Marine for the prevention of goiters in endemic regions would also undoubtedly control the incidence of substernal goiter. Where symptoms of mediastinal compression are severe, we have recourse to two methods of treatment. The first is deep roentgen therapy, which has been beneficial in a few reported cases, and second, surgical interference when the former fails. The latter should be resorted to only in those cases where the symptoms are grave and failed to respond previously to conservative methods of treatment.

* It has been our good fortune to reëxamine patient R. de S., on November 23, 1925. Her general condition is excellent. There remains a slight residua of distended veins of her left arm and some signs of hypothyroidism. The teleroentgenogram shows a difference of 2 cms. in the size of the shadow in the transverse diameter, *i. e.*, 12 cms. on previous examination, and 10 centimeters to date.

Conclusions. 1. Substernal thyroid is more frequent than is usually believed.

2. Any shadow in the upper mediastinum, which shows a distinct line of demarkation, and is separate from the aorta, is usually a retrosternal goiter.

3. Fluoroscopic examination reveals the absence of expansile characteristics.

4. The mass moves with the trachea during respiration.

5. A visible goiter, plus signs of compression; or signs of compression, plus thyrotoxic symptoms, are indicative of a substernal goiter.

6. Auricular fibrillation associated with indications of a mass behind the manubrium sterni points toward the existence of a substernal thyroid.

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PROGNOSIS IN EXOPHTHALMIC GOITER.

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This report is based on the findings in 100 cases of Graves' disease seen by the writer during the past six years. Being purely a clinical study, consideration of pathology in those cases where pathological material was obtained will be reserved for a future communication.

Definition. Neither Parry, when he described 8 cases one hundred years ago, nor Graves, who described 4 cases ninety years ago, gave a definition of this interesting disease. Since confusion often arises through failure to define terms, it seems advisable to

state what I mean by exophthalmic goiter thus: A constitutional disease of unknown etiology, exhibiting as major characteristics tachycardia, elevated basal metabolic rate, goiter and exophthalmos, these being accompanied in most cases by one or more of the following: Tremor, nervousness, insomnia, weight loss, sweating, pigmentation, vomiting, diarrhea and mental aberration. This definition excludes toxic adenoma, though tachycardia and increased metabolic rate are constantly present in both conditions.

Clinical Features. The firmly established and universally recognized clinical points in this disease may be summarized as follows: It occurs at all ages and in all parts of the world, though its incidence seems to be greater in goiter districts. It is about nine times more frequent in females than in males. It is prone to run a cyclic course with remissions and recrudescences,[1, 2, 3] and has a tendency toward chronicity, though it frequently results in spontaneous recovery, which facts render the evaluation of therapeutic procedures rather difficult. It presents atypical forms and there is an irreducible minimum of mortality.

The most constant feature of this disease, without which the diagnosis is never justified, is an elevated basal metabolic rate. When accurately determined it furnishes a reliable objective, quantitative estimate of the severity of the disease. Utilization of this diagnostic aid was a constant feature in the study of all cases in this series, a total of over four hundred determinations being made on 100 patients.

Data. It was deemed advisable to consider separately the cases of those patients who had submitted to surgical intervention prior to coming under my observation. In addition to illustrating a frequent result of one form of treatment, they possess in common chronicity and similar prognostic and therapeutic features. The cases in which prior surgery was not a factor were arbitrarily subdivided into two groups—one the typical, the other the atypical cases.

The first group comprises 56 typical cases, with basal metabolic rates from +22 to 112 and an average of +54, as shown in Table I. There were 11 males and 45 females, the relatively high percentage of men being due to the fact that the U. S. Veterans' Bureau furnished a number of men in the series. Though the main features are given in Table I, such a mode of presentation is inadequate to bring out all that is to be learned from such a series. Of the 6 deaths, 4 occurred in patients who were operated upon. These will be discussed later under the head of "surgery." The other 2 were cardiac deaths in patients who were fibrillating since first coming under observation. One of these was a man, aged fifty-seven years, who, according to his history, had suffered from this disease since the San Francisco earthquake in 1906. Three of the cases in this group have been reported in detail elsewhere.[4]

TABLE I.—EXOPHTHALMIC GOITER. GROUP I (56 CASES).

Sex.	Age	Duration of symptoms before M.D. was consulted, years.			Basal Metabolic rates.*						Treatment.							Result.				
					First.			Last.														
	Ave.	Av.	Max.	Min.	Av.	Max.	Min.	Av.	Max.	Min.	Surgery.	Roentgen-ray.	Iodin.	Rem. foc. infs.	Ovarian extr.	Thyroid extr.	Salvarsan.	Cured.	Improved.	Not improved.	Died.	No follow up.
Female (45)	37	1½	7	1 mo.	55	112	22	17	60	−16	10	35	14	2	1	2	..	20	18	2	5	1
Male (11)	38½	3¼	15	1 mo.	53	70	25	27	60	3	4	5	2	2	—	0	1	3	5	1	1	0
Total (56)	37¼	2	..	....	54½	...	..	20	..	....	14	40	16	4	1	2	1	23	23	3	6	1

ATYPICAL EXOPHTHALMIC GOITER. GROUP II (19 CASES).

Female (17)	32	1½	4	1	25	65	−18†	14	29	5	1	9	3	2	0	0	0	13	3	..	1	
Male (2)	36	..	..	..	30	40	21	16	23	9	0	2	0	0	0	0	0	..	1	..	1††	
Total (19)	32½	..	..	..	25½	..	..	14¼	..	..	1	11	3	2	0	0	0	13	4	..	2	

* The signs of all B. M. R. readings are plus unless indicated as minus. (Tables I and II).

† At an examination nineteen months later this patient's B. M. R. was +15 per cent. †† "Lost at sea."

The second group consists of 19 mild and atypical cases, summarized also in Table I. The outstanding symptoms presented by the patients in this group were: Tachycardia, nervousness and loss of weight. None of these had exophthalmos nor the classical signs of exophthalmic goiter, though many had slight enlargement of the thyroid gland. All had elevations of the basal metabolic rate varying from +13 to +65 before treatment. Since none of these patients had exophthalmos and only a few had goiter, the appellation, "exophthalmic goiter," might be disputed. With persistent elevation of the basal metabolic rate and many of the other classical signs of this disease, without other evident cause for the condition, one must make the diagnosis of exophthalmic goiter.

None of these cases fell under the classification of effort syndrome or irritable heart, for they all had elevation of the basal metabolic rate and, furthermore, the outcome in most of these cases was cure in from three months to a year. Some of this group ran the typical course of remissions and recrudescences so characteristic of this disease, those with the higher rates tending to run a longer course and more nearly approaching the typical case of the first group. In fact, the division line between the two groups is purely arbitrary for the 75 cases could be arranged in a continuous series beginning with the severe cases, most of which had the fully developed picture, and ending with the mild cases which were for the most part atypical. In the atypical, or mild cases, the prognosis is favorable for complete recovery under ordinary symptomatic treatment, neither roentgenotherapy nor surgery being required, though the former was used in 11 of these cases and one thyroidectomy was performed on a patient whose metabolic rate was only +13.

There was 1 death in this group, a physician's wife, aged thirty-six years, who had a persistent hypertension (systolic, 186 to 222; diastolic, 150 to 160), taken always under basal conditions while resting between two determinations of her oxygen consumption. The basal metabolic rate ranged from +19 to +41. There were six estimations made between March 28, 1923, and April 23, 1924, during which period she had a remission of her symptoms, though she died about six months after the last recorded date. This patient fits the description of 5 cases recently reported by Boas and Shapiro,[5] all of whom had hypertension and elevation of the metabolic rate. In view of the frequency of hypertension, I do not believe that there is sufficient evidence to justify the hypothesis that these cases represent more than the chance association of two unrelated conditions.

Group III consits of 25 patients whose thyroids had been operated upon before coming under my observation. Their basal metabolic all rates varied from —7 to +80, as shown in Table II. They all presented some of the signs or symptoms for which thyroidectomy

had been performed, and for which they sought further relief. That they originally had Graves' disease was determined from the evident persistence of some of the classical features or statements from the operator or patient that this disease existed prior to operation. Four of these cases have already been reported in detail.[4, 6]

The first fact demonstrated by this group is that thyroidectomy (subtotal in many of the cases) does not always produce a cure, although it usually results in some improvement. The second evident fact is the chronicity of this disease in some patients. It is assumed that persistence of the condition is in spite of surgery, not because of it, for it seems to be true that in some cases the signs and symptoms become chronic regardless of any or all treatment. Iodin was found to be the most potent therapeutic weapon in treating the patients in this group.

Surgery. In addition to the 25 patients of Group III, 16 patients of Groups I and II submitted to surgical intervention, all being thyroidectomized, except 1 who had double ligation. Five of these 16 died; 3 in acute "thyroid crises;" 2, twenty-four and forty-eight hours after operation. One died three months after double ligation while waiting to reach a condition favorable for thyroidectomy. The fifth succumbed five months after a second thyroidectomy which reduced him to a state of myxedema and tetany. The 16 operations represent the work of eight surgeons, all of whom are skilled operators, yet the mortality rate in this group is 31 per cent. Kessel and Hyman[7] report an immediate operative mortality rate of 9.3 per cent in 43 subtotal thyroidectomies. These figures suggest the probability that surgical treatment of exophthalmic goiter throughout the whole United States is attended by a mortality rate which is several times the very low rates reported from a few of the best thyroid clinics in this country.

My experience with surgery in exophthalmic goiter, both from the standpoint of mortality rate and results, is such as to dampen any enthusiasm I might otherwise have for this form of therapy. Perhaps my experience has been peculiarly unfortunate. Nevertheless I am moved to report the 25 cases previously operated on, which I regard as surgical failures, because they constitute a type of case frequently encountered but seldom reported. While recognizing the fact that surgical measures failed to restore these patients to health, it is my belief that they belong to the class of chronic cases which are never cured. Some, perhaps many of them, were medical failures before they became surgical failures. No criticism of the surgery is offered for some of these patients had journeyed to the best thyroid clinics in the country, while others had expert surgery in this vicinity (Table II).

TABLE II.—PRIOR SURGICAL TREATMENT. GROUP III (25 CASES).

No.	Age.	Sex.	Operation.			Major presenting complaint.	B. M. R.				Treatment.	Result.
							First.		Last.			
			Date.	Place.	Type.		Date.		Date.			
1	40	F.	2/1918	S. F.	Lobectomy	Weight loss	3/22/22	74	9/25/23	33	Roentgen-ray, iodin	Moderate improvement.
2	30	F.	1920	Colorado	Double lobectomy	Fast heart, nervous	11/ 4/22	11	.....	..	.....	No follow up.
3	35	M.	4/16/21	S. F.	Partial thyroidectomy	Weight loss, nervous	12/15/21	38	4/22/22	−9	Total thyroidectomy	Death.
4	38	F.	11/15/19	S. F.	Partial thyroidectomy	Fast heart, nervous	9/19/23	80	5/ 5/24	4	Roentgen-ray, iodin	Accidental death.
5	26	F.	1917	San Jose, Calif.	Partial thyroidectomy	Fast heart, weakness	10/27/20	24	8/30/24	5	Iodin, roentgen ray	Cured.
6	58	F.	1912	S. F.	Lobectomy	Fast heart, headache	11/27/21	−6	3/25/25	3	Rest	Improved.
7	53	F.	4/22 6/22	S. F. S. F.	Ligations, thyroidectomy	Nervous	11/11/22	33	7/10/25	13	Roentgen-ray, iodin	Slightly improved.
8	46	M.	1912 1913	Rochester, Minn.	3 ligations, hot water injections. Two lobectomies	Weakness, fast heart	9/27/22	49	6/ 4/24	23	Roentgen-ray in 1913, iodin 1924	Improved.
9	36	M.	2/20 5/20	S. F.	Ligations, subtotal thyroidectomy	Weight loss, fast heart	3/17/25	42	6/13/25	86	Roentgen-ray, iodin	Worse.
10	42	F.	1914	S. F.	Lobectomy	Weight loss	8/20/21	16	9/27/24	65	Iodin, induced menopause	Worse.

11	33	M.	11/20	S. F.	Lobectomy	Weight loss	10/10/24	40	12/ 2/22	47	Roentgen-ray	No change.
12	32	M.	1919	S. F.	Lobectomy	Fast heart, nervous	7/18/22	29	.....	..	.....	U. S. Vet's., rating 50 per cent.
13	36	F.	1914	S. F.	Thyroidectomy	Fast heart, nausea	8/11/22	3	.....	..	Roentgen-ray '16, ovarian ex.	Improved.
14	35	F.	3/24/21	S. F.	Subtotal thyroidectomy	Weakness, fast heart	6/14/21	16	7/ 8/21	−2	Roentgen-ray	Improved.
15	29	F.	4/1920	Minnesota City–?	Partial thyroidectomy	Fast heart, weight loss	3/31/24	−1	4/15/24	16	Iodin	Improved.
16	29	F.	1920	S. F.	Lobectomy	Fatigue	10/11/21	26	11/23/21	−4	Roentgen-ray	Improved.
17	32	M.	4/1920	U.S.P.H.S.	Lobectomy	Fast heart	6/12/22	0	.....	..	.....	Cured.
18	34	F.	11/1920	S. F.	Subtotal thyroidectomy	Fast heart, nervous	3/ 2/21	14	.....	..	.....	Suicide (?)
19	43	F.	1914	Rochester, Minn.	Partial thyroidectomy	Nervous	12/16/22	14	5/23/23	36	.....	No change.
20	40	F.	9/1915	New York	Partial thyroidectomy	Nervous	3/ 7/23	1	.....	..	Roentgen-ray	Improved.
21	51	F.	1911	Cleveland (Crile)	?	Nervous fears	8/31/23	−2	.....	..	Thyroid, ovarian ex.	No change.
22	36	M.	1917	Chicago	Thyroidectomy	Cough, abdominal pain	11/28/23	16	.....	..	.....	No follow up.
23	28	M.	1/1922	?	Ligation	.....	8/1922	20	1/13/23	4	.....	No follow up.
24	23	F.	8/26/21	S. F.	Right lobe and isthmus	Fast heart, nervous	7/15/22	−7	.....	..	.....	Improved.
25	29	F.	1914	Rochester, Minn.	Thyroidectomy	.....	9/27/24	7	.....	..	Iodin, ovarian ex.	Improved.

Prognosis. Search of the literature fails to yield much information regarding prognosis in exophthalmic goiter, nearly all statements being colored by the writer's theory of etiology or more particularly the result of the form of therapy administered. The most helpful work elucidating this point recently was that reported by Kessel, Hyman and Lande.[8] They observed the course of this disease in a series of patients who were given only symptomatic therapy and reported results which vary but little from those obtained when elaborate and detailed therapeutic procedures were followed.

Some rather extensive and illuminating figures upon which one may base some ideas of prognosis were published by Hale-White[9] in 1910. He reported 226 cases, including all of those (169) admitted to Guy's Hospital from 1888 to 1907 and 57 private patients seen from 1894 to 1909. Exclusive of 3 patients, who died directly from operative procedures, the immediate mortality rate among the other 166 hospital cases was 10.7 per cent. In the whole series 11 patients were operated upon with 4 immediate deaths. He classified 65 per cent of the whole number as "mild or average," 24 per cent "severe," and 11 per cent "very severe," and makes the interesting observation that the ultimate outcome of the case did not depend on the severity of the disease when the patient was first seen for some milder ones ran long courses and were never cured, while 8 hospital and 17 private cases grouped as severe or very severe have done well. He believes that the social status is a very important factor, because the percentage of recoveries was much higher among the private than among the hospital cases, though both groups were of equal severity, most of the private cases being seen in consultation. Exclusive of 22 deaths while still under observation, there were traceable 110 patients of whom 70 per cent "got quite well," 24 per cent "were much better" and 6 per cent "were better in some respect or other." Actuarial calculation showed that the death rate for patients with this disease is about twice that of normal females of the same age, but as the latter is not high for this age (thirty to forty-five years), the mortality among patients with exophthalmic goiter is not excessive. The ratio of males and females in this series was 1 to 11.

Hale-White's work is very valuable, it seems to me, as it furnishes data on the later course of the disease. Though his patients received more symptomatic treatment than did those of Kessel and others, still it is probable that the bed rest was the most valuable, though it probably did not affect the course of the disease, as is sometimes possible by iodin, Roentgen ray or surgery. The elapsed time is quite sufficient to demonstrate that most patients recover from Graves' disease, and that the mortality rate is not high.

In the Bradshaw Lecture for 1916 Hector Mackenzie[10] sums up

prognosis in exophthalmic goiter as follows: "There is reason to believe that in about 25 per cent of the cases death results from the disease, and that under ordinary medical treatment in about 50 per cent more or less complete recovery will eventually take place, while in the remainder the disease continues in a chronic form during life."

From a survey of this series one gathers the following impressions regarding prognosis, which are in accord with the findings of the authors just cited: Some cases run a course to spontaneous recovery, some will die in spite of all therapy and some because of it. The chief concern with the first class is to avoid therapeutic procedures which will bring about a fatal termination. The mortality rate in this series is 11 per cent. Ten of the deaths have been discussed already. The eleventh was due to veronal poisoning, probably suicidal. Exclusive of 4 deaths directly due to surgery, the mortality rate is 7.3 per cent, and further deducting 3 accidental deaths it is 4.3 per cent.

Thirty-eight per cent seem to be cured and about 21 per cent are sufficiently improved as to be restored to full social and economic usefulness. The remaining 30 per cent, which includes 23 of the 25 patients previously operated upon, will be sufferers from the disease or its sequelæ the remainder of their lives. The tendency for this disease to become chronic in certain instances is a feature which has not been sufficiently stressed. However, recognition and emphasis of this, and also the fact that this disease runs a fairly characteristic course and often ends in spontaneous recovery, must not be interpreted as indicating an attitude of therapeutic nihilism. Some writers, Leonard Williams for example, are inclined to doubt "Whether in pronounced cases recovery is ever complete." The chronicity in many cases lends support to that opinion. But what constitutes a pronounced case is not always easy to determine. The metabolic rate is the most valuable aid, but patients with very high rates may run a short course to satisfactory recovery. Those conditions which are universally conceded to augur ill for the patient are gastrointestinal symptoms in particular, and mental aberration, which is often permanent.

The acute fulminating cases with high metabolic rates, hyperthermia, dysentery, vomiting and mania, are fortunately rare. I have never seen one, but should I be called to express an opinion upon such a case I should consider the prognosis unfavorable for recovery and anticipate an early exitus.

Sex. As to sex in relation to prognosis, this survey seems to show that males are more resistant to treatment of all kinds, and there is greater likelihood of the disease becoming chronic than in females. The U. S. Mortality Statistics for the twelve years from 1910 to 1921, inclusive, report 11,212 females and 1532 males as having died from exophthalmic goiter. This is a ratio of 1 male

to 7.32 females, which is a slightly higher percentage of males than is reported in most series in the literature. This might be taken to indicate a higher mortality rate among males. There were 20 males in this series, of whom 3 are dead. One is reported simply as "lost at sea;" 1 is the already-mentioned long-standing case with auricular fibrillation and death from cardiac failure; the third was a beneficiary of the Veterans' Bureau, who died of tetany and myxedema following a second thyroidectomy. Of the remaining 17 men only 3 can be classified as cured.

Age. Age does not seem to be such an important factor as some writers believe. The average age in all three groups of this series is about thirty-seven years for both sexes. The youngest patient was a girl, aged thirteen years, who presented quite a typical picture, though the metabolic rate was never more than +22. She has entirely recovered one year after thyroidectomy, a procedure which I believed was unnecessary in her case, as her trouble seemed to be associated with the onset of menstruation, and she improved and gained 20 pounds in two months after iodin therapy. The oldest patient was a woman, aged sixty-four years, whose first basal metabolic rate was +78. This had dropped to +11 twenty-three months later, at which time she was encountered in a hospital corridor working as a maid. One other patient, a woman, aged sixty years, made a complete recovery in a year. Both these patients received roentgenotherapy.

Menopause and Pregnancy. It has been stated that women who developed Graves' disease at the menopause have a prognosis unfavorable for recovery. That has not been my experience, though I have seen a number of patients suffering from this disease at the time of the climacteric. Causing cessation of menstruation by roentgenotherapy is often a therapeutic measure of great benefit in this type, which fact suggests that the signs of thyroid disturbance are a part of the glandular readjustment at this time of life.

Pregnancy is a serious event in this disease, often precipitating a crisis, and many cases have their onset at this time. One case of this series illustrating this point has been reported previously.[6] It is questionable if a woman who has had this disease should become pregnant. No better test of cure exists than to go successfully through a pregnancy.

Time Element. An interesting point revealed in the study of the individual case histories in this series, and one of some significance, is the long duration of symptoms before medical aid is sought. Fortunately this is not an incapacitating disease; in fact, in the early stages the patient feels exhilarated. As a consequence, patients frequently do not seek aid for many months or years. A study of this point was made, and it was discovered that the average duration of symptoms before visiting a physician was one year and

two months in those patients classified as "cured" and two years and six months in those patients who can only be called "improved."

The former seem to be acute cases with fairly well-defined onset, rapid progress and prompt recovery. These patients may be very ill, with metabolic rates as high as +80, and lose considerable weight. The thyroid is often only slightly enlarged. The prognosis is favorable for recovery under any intelligent treatment.

The chronic type has a more insidious onset, often preceded for years by thyroid enlargement. One might think that they were acute cases which did not receive treatment and had become chronic, but I do not believe this to be a fact, for many acute cases run a short course to spontaneous recovery without treatment, and this chronic type of case continues resistant to therapy even when seen fairly early in its course.

Causes of Death. Death in exophthalmic goiter is generally by one of two routes: First, acute crisis, which may terminate a case only a few days after its onset, or it may develop without apparent cause in a long-standing case. Such an exitus was a too frequent occurrence following thyroidectomy in the days prior to preoperative preparation by saturation with iodin. Three of the surgical deaths in this series were of this type, the pulse rates going to 176 to 182 and temperatures to 41.2° C. just before death.

The second manner of demise is by cardiac failure, which is most often preceded for many years by auricular fibrillation. It is unnecessary to dwell here upon this effect of the disease, for Kerr and Hensel,[11] Levine and Sturgis,[12] Hamilton,[13] Dunhill, Fraser and Stott[14] have all written recently upon the cardiac complications and sequelæ of this disease. Damshek[15] reviewed the subject completely last year and compiled a bibliography of eighty-four references.

Cardiovascular Complications. Six patients in this series had fibrillation. Three are dead, 1, however, being killed in a street accident. Of the other 3, 1 was still fibrillating four years after discharge, though she had apparently recovered from the Graves' syndrome, and was not decompensated. One did not reply to my questionnaire and the sixth is doing well. Willius, of the Mayo Clinic, states that 7 per cent of patients with exophthalmic goiter go into auricular fibrillation.

A more frequent type of irregularity encountered in this group was ventricular premature systoles, which seem to occur in nearly all patients with Graves' disease at some time in its course. They do not materially affect prognosis unless accompanied by other signs of myocardial change.

Of more value prognostically is the blood pressure. Leaving out of consideration the atypical cases with marked hypertension already mentioned, I believe that patients with high systolic and relatively high diastolic pressures do not recover so quickly as those

with lower pressures. It has been previously noted elsewhere[16] that with increased oxygen consumption a wider pulse pressure is the rule. This widening of the pulse pressure is generally accomplished by lowering the diastolic and elevating the systolic pressures. But in patients who appear to have difficulty in making this seemingly physiological adaptation the course of the disease is not so smooth or so short. I recall one patient in particular, a young woman, aged twenty-three years, who has now entirely recovered, but who ran a very obstinate course and had blood-pressure readings which were constantly high. Troell,[17] a Swedish worker, has made some studies on blood pressure in this disease, and believes that marked deviations from the normal relationships which exist between systolic, diastolic and pulse pressure are of prognostic value.

The frequent, perhaps constant, occurrence of damage to the cardiovascular system in this disease presents a serious problem to the clinician and to prevent this damage is his chief concern in endeavoring to shorten the course of the disease as much as possible. Prevention of cardiac damage is the strongest argument for surgical intervention, and if this desirable end were more frequently accomplished some of the unfavorable aspects of this therapeutic procedure would be counterbalanced.

Conclusions. 1. Acute cases of exophthalmic goiter with well-defined onset offer a more favorable prognosis for recovery than those with insidious onset and symptoms existing for several years before seeking medical advice.

2. The height of the basal metabolic rate offers only slight assistance in estimating the prognosis.

3. Males with exophthalmic goiter seem more resistant to treatment and are more apt to become chronic sufferers than are females.

4. Subtotal thyroidectomy nearly always produces a remission of the disease if the patient survives the operation, but it does not constitute a cure.

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TOTAL THYROIDECTOMY IN THYROTOXICOSIS OF THE EXOPHTHALMIC TYPE. A PRELIMINARY REPORT.

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From the observation extending over a number of years of a large number of patients suffering from thyrotoxicosis of the exophthalmic type treated by the usual surgical measures we were impressed that the recovery of many was decidedly incomplete. We also noted that the greater the amount of gland removed at operation the more complete the cure of the patient.

We argued that in this condition the entire thyroid gland is diseased and should be removed. For a diseased gland could then be substituted the extract of a normal gland. We decided therefore upon complete removal of the thyroid in thyrotoxicosis of this type and administration of thyroid extract.

We have also observed in a number of cases that the greater the amount of thyroid gland removed at operation the less the reaction, the shorter the period of convalescence and the sooner the patient was able to resume his occupation. More important still these individuals did not relapse.

Each of the individuals making up this series had been under treatment for from one to eight years, was suffering, and was absolutely incapacitated from useful pursuits during these periods.

In addition each was classed as incurable and was considered a poor operative risk.

Ten patients form the basis for this preliminary report and of these, 7 had been under continuous medical supervision including the usual methods indicated by that term from one to eight years. Each of these 7 had received numerous Roentgen ray treatments, 2 as many as sixty.

To each patient, before subjecting him to a total thyroidectomy, our object was carefully explained as was the fact that they would have to take a certain daily amount of thyroid preparation for the remainder of their lives. No difficulty was experienced in obtaining the patient's consent as all of this group of individuals were hopeless invalids.

The operation consisted in removing the entire thyroid gland, the safety of the parathyroids and recurrent laryngeal nerves being insured by shaving the posterior portion of each lateral lobe as close to the capsule as possible. All but 2 patients received iodin both before and after the operation.

Case Reports. CASE I.—D. H., aged fifty-six years, male, with thyrotoxicosis of the exophthalmic type, had been totally incapacitated for three years. The basal metabolic rate was +43 per cent, the pulse 120 per minute; there was marked nervousness and tremor, shortness of breath and great fatiguability.

This patient presented a pitiful appearance with his extreme nervousness and lack of concentration. His markedly prominent eyes, marked tremor and loss of weight had kept him from any gainful occupation for three years. He had received forty Roentgen ray treatments and courses of iodin in addition to the usual medical measures.

A total thyroidectomy was followed by slight postoperative reaction and an uneventful convalescence.

The patient's condition demanded thyroid extract, 1 gr. daily, three weeks following the operation. His basal metabolic rate at that time ranged from −5 per cent to +2 per cent and his pulse rate from 60 to 72 per minute.

At present, one year after the operation, this patient has gained 17 pounds in weight, feels perfectly well, has no symptoms and has been at work steadily since two months after his operation. His exophthalmos disappeared promptly. His basal metabolism is normal, his pulse 72 per minute. He requires 1 gr. of thyroid extract daily. He has been at work for nine months.

This patient is now calm, full of energy and averages 3 miles walking daily at his occupation of insurance broker.

CASE II.—W. L. B., aged fifty-four years, male, with thyrotoxicosis of the exophthalmic type, suffered total incapacity for four

years. The basal metabolic rate was +45 per cent, the pulse rate 120 per minute; the hands were moist and warm; tremor was present, also marked fatigue and shortness of breath.

This patient's vital capacity was but 50 per cent and shortly before operation on his attempting to work he became seriously ill and lost 40 pounds in weight.

As with the first case, this patient's condition was considered hopeless. He looked extremely ill and emaciated, had been unable to earn a living for over four years during which period he had been continuously under treatment. Definite cardiac decompensation was present with shortness of breath and swelling of the feet. He received a total of fifty Roentgen ray treatments and iodin in addition to the usual medical measures.

A total thyroidectomy was followed by no postoperative reaction and by a rapid and uneventful convalescence with disappearance of exophthalmos.

The basal metabolic rate fell to −16 per cent within a month after operation with symptoms of hypothyroidism. Thyroid extract was administered and the basal metabolic rate brought up to normal by thyroid feedings. He has no tremor.

Nine months later this patient is feeling well; his pulse is 72 per minute, his weight is 170 pounds—a gain of 40 pounds—and he has resumed his occupation of carpenter. He receives at present 2 to 3 gr. of thyroid extract a day. After a hard day's work at carpentering he walks for exercise, sleeps well, eats well and is happy.

CASE III.—A. H., aged twenty-eight years, female, married, had thyrotoxicosis of the exophthalmic type, with total incapacity for six years. The basal metabolic rate was +44 per cent, the pulse rate 116 per minute; there was marked nervousness and tremor, great fatiguability and loss of weight.

This patient's nervousness and exophthalmos were extreme as was her fatiguability. She had been unable to perform her household duties for six years. She received Roentgen ray treatment off and on for over a period of three years, iodin, and so forth.

A total thyroidectomy was followed by practically no reaction and an uneventful convalescence.

Following operation the patient's metabolic rate fell to −16 per cent after a month. The rate was brought up slowly by means of thyroid extract, the maximum being 3 gr. daily. Now the patient feels perfectly well, has gained 14 pounds, her pulse rate is 70 per minute, she feels strong and is able to do her housework, which she has been unable to do for years. Her exophthalmos has disappeared. She has been well since her operation ten months ago.

CASE IV.—G. C., aged forty-nine years, male, had thyrotoxicosis of the exophthalmic type, with nervousness, fatiguability and

weakness for the past year. This patient did not respond to rest and iodin and on account of his poor condition was subjected to ligation of both superior thyroid vessels. This did not appreciably alter his general condition or lower his basal metabolic rate. The latter remained above + 80 per cent and his nervousness and motor activity were most marked. He was completely incapacitated from work and his motor nervousness was so great he was unable to recuperate by rest.

A practically total thyroidectomy was done, a portion of the lower left lobe, 1 by 1 cm. in size, being left. This operation was followed by no more, if as much, reaction than followed the ligation operation and patient's convalescence was uneventful and prompt.

The basal metabolic rate fell eleven days following the operation to + 22 per cent. The pulse rate dropped to normal, the nervousness had disappeared as had the exophthalmos and the patient had resumed his occupation within two months. He is still at work and feels well. He has failed to report for three months for a basal metabolic reading but sends word he feels well and is hard at work as a contractor.

CASE V.—G. T., aged forty-five years, female, married, had thyrotoxicosis of the exophthalmic type, with total incapacity for three years. The basal metabolic rate was + 60 per cent, the pulse rate 130 per minute; there were nervousness and tremor, fatiguability and loss of weight.

This patient was a thin, emaciated, nervous little woman showing marked fatiguability with despondency and discouragement. The usual measures, with the exception of iodin, were tried.

A total thyroidectomy was followed by a moderate reaction only, and an uneventful convalescence.

A month later her basal metabolic rate was − 21 per cent and was readily brought up to normal by thyroid extract. The patient gained rapidly in weight, felt and looked like a young woman and was able to carry on rather strenuous housework. At present the pulse is between 68 and 72 per minute and she feels well. She is now, a year and a half after operation, receiving 1 gr. of thyroid daily and is well.

CASE VI.—F. S., aged twenty-seven years, male, had thyrotoxicosis of the exophthalmic type. This patient was incapacitated for three years and hospitalized for one year and received sixty Roentgen ray treatments and several courses of iodin during that period. His basal metabolic rate was + 50 per cent, fatiguability was marked as was the patient's nervousness and tremor. He had lost a large amount of weight.

A practically total thyroidectomy was followed by no postoperative reaction and an uneventful rapid convalescence.

Within a month this patient was able to resume his studies at college. His basal metabolic rate was maintained at normal with periodic feedings of thyroid extract. When last heard from, a year after the operation, this patient was apparently perfectly well and extremely grateful.

CASE VII.—C. W., aged thirty-four years, female, married, had thyrotoxicosis of the exophthalmic type. This patient had been subjected to subtotal thyroidectomy eleven years previously. She did fairly well until two years ago but never lost her exophthalmos completely or her rapid pulse.

During the past two years the patient had a return of symptoms and before the present operation showed marked exophthalmos, a pulse rate of 120 to 130 per minute permanently, nervousness and great fatiguability with shortness of breath.

A practically complete thyroidectomy was followed by no postoperative reaction and a rapid uneventful convalescence. A piece of thyroid gland, approximately 1 by 1 cm., was left.

At present, one year after her operation, she looks and feels well, exercises vigorously, and her pulse rate is between 70 and 80 per minute. The exophthalmos has completely disappeared.

This patient passed through two experiences two months ago that apparently upset her not at all. She was operated on for pelvic trouble and later did vigorous work saving personal belongings when her house caught fire. Following these experiences the patient reported to see if she had injured herself. She was found to be, apparently, perfectly well.

CASE VIII.—H. W., aged forty-two years, female, single, with thyrotoxicosis of the exophthalmic type, showed markedly prominent eyes, extreme nervousness, tremor, loss of 40 pounds in weight and had been incapacitated practically for the past eight years and completely for the last two.

The lowest point attained by the basal metabolism after medical treatment, including Roentgen ray, rest and iodin, before coming to our clinic was +30 per cent.

A total thyroidectomy was followed by an uneventful convalescence with no postoperative reaction.

One week after the operation the patient's basal metabolic rate was −6 per cent. This was brought up to normal with 1 gr. of thyroid daily. At present, three months after the operation, she feels well, her pulse is 68 per minute, her nervousness has practically disappeared and she has gained 8 pounds in weight. The patient feels very grateful.

CASE IX.—E. W., aged nineteen years, female, single, had thyrotoxicosis of the exophthalmic type. This young woman had

been ill for two years. She showed a very marked nervous reaction, moderate exophthalmos, marked tremor with warm, moist palms and was incapacitated.

The basal metabolism was +42 per cent, the pulse varied from 110 to 130 per minute, and the condition resisted the usual medical measures, including Roentgen ray and rest.

A total thyroidectomy was followed by a moderate reaction as shown by a postoperative temperature of 101. Patient's convalescence was uninterrupted. Her basal metabolism was −5 per cent two weeks after the operation and she was given a ½ gr. of thyroid extract daily.

Six weeks only have elapsed since this patient was operated on but she already looks and acts like a different person. Her pulse is 74 per minute, she has gained weight, feels well and strong and her exophthalmos has nearly completely disappeared. She shows no tremor and her skin is of normal temperature.

CASE X.—S. M., aged twenty-six years, female, married, had thyrotoxicosis of the exophthalmic type. The patient was incapacitated from performing her household duties for about one year. She was nervous, had lost some weight and tired readily. On examination there was found some prominence of the eyes and stare, tremor and a pulse of 110 per minute.

A total thyroidectomy was done. This patient had been a trained nurse previous to her marriage and preferred surgery. Her convalescence was uneventful and the operation followed by no untoward reaction.

Shortly after the operation her basal metabolism was −14 per cent. She was given thyroid extract, 1 gr. daily, which restored her basal metabolism to normal.

At present, three months after the operation, the patient is well, feels cheerful, is able to work and has a pulse rate of 70 per minute.

In all of the cases the operations were performed with the patient under light nitrous oxid and oxygen anesthesia and both sides of the neck were blocked by injecting 0.5 per cent novocain previous to the incision.

Conclusions. 1. In selected cases at least, a total thyroidectomy is indicated. For all cases requiring operation a much larger amount of thyroid gland should be removed than is at present usually done as we believe the entire gland is diseased and normal should be substituted.

2. The postoperative reaction appears to be inversely proportionate to the amount of gland removed. This apparently applies likewise to the period of convalescence.

3. It is not difficult in cases of total thyroidectomy to maintain a proper thyroid balance with a thyroid preparation, if regulated from time to time by basal metabolic determinations. A number

of these patients are able to determine subjectively the amount of thyroid extract they require.

4. In seemingly hopeless cases of exophthalmic goiter the results of total thyroidectomy have been most gratifying. The patients after long periods of complete invalidism have resumed their usual occupations and enjoy good health. While we have confined total thyroidectomy for the most part to those patients who were seemingly hopeless and had been invalids for long periods of time, we feel that the procedure may be extended to embrace less severe cases. We feel this because: (1) The entire gland is diseased; (2) the amount to be removed is indeterminate and the subsequent action of the amounts of gland remaining is likewise indeterminate.

5. We realize the number of cases upon which this report is based is small. However, the uniformly good results appear to warrant this preliminary communication.

THE DIAGNOSTIC CRITERIA OF CHRONIC PARATHYROID INSUFFICIENCY WITH SPECIAL REFERENCE TO THE PHOSPHATE CONTENT OF THE BLOOD.

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Although the first definite description of the parathyroid glands was that of Sandstrom, a Swedish anatomist, in 1880, it has been pointed out by Walter Edmunds that there is in the Museum of the Royal College of Surgeons a specimen showing the parathyroid glands as well as the thyroid glands of the Indian rhinoceros. It was obtained in 1849, when the animal died in the Gardens of the Zoölogical Society of London. Sir Richard Owen reported the results of its dissection to the society in 1850. He described a small compact yellow glandular body attached to the thyroid at the point of emergence of the veins. This seems to have been the first anatomical description of the parathyroids as separate and individual organs.

After Sandstrom's description of the parathyroids, Weiss, in Billroth's Clinic in Vienna, reported the occurrence of tetany in some patients after removal of the thyroid for goiter, and named the conditions tetania strumipriva. In 1891 Gley showed that no tetany occurred in rabbits when the thyroid was removed. However, he misinterpreted his findings regarding the parathyroids as part of the hypertrophic mechanism of the thyroid. In 1896–1897 Vassale and Generali established definitely the distinction between the effects of removal of the thyroid as myxedema, or cachexia

strumipriva, and the effects of removal of the parathyroid as tetany. They therefore proved the existence of functional difference between the two organs as of structural difference. A number of subsequent observers and experimenters confirmed their observations.

The occurrence of tetany therefore became the criterion of parathyroid insufficiency. The peculiar spontaneous attacks of tonic spasm in the extremities causing them to assume characteristic attitudes became pathognomic. It was soon found that individuals with tetany of the extremities could also have spasms of the whole body musculature. Then it was found that these spontaneous attacks occurred in individuals who between attacks presented a specific hyperexcitability of the nervous system, and that tonic spasms could be provoked by various stimuli, preferably mechanical or electrical. This condition was described as latent tetany.

TABLE I.—COMPARISON OF ELECTRICAL IRRITABILITY OF ULNAR NERVE—CHVOSTEK REACTION, NORMAL BLOOD CALCIUM AND INCREASED BLOOD PHOSPHATE—IN CASES OF SUPPOSED PARATHYROID INSUFFICIENCY.

	Name.	K O C	K C C	A O C	A C C	Chvostek	Blood calcium.	Blood phosphate.
1	H. E. B.	3.9	1.2	1.1	2.8	xxx	12.4	3.0
2	F. S.	2.4	1.1	0.9	1.9	xx	11.8	5.1
3	M. F.	2.5	1.0	0.9	2.1	xx	9.6	5.0
4	E. K.	2.8	1.4	1.2	2.3	xx	10.4	5.1
5	F. C. M.	2.5	1.2	1.3	2.4	xxx	10.2	5.4
6	E. K.	4.0	1.9	2.5	3.8	x	10.2	4.5
7	J. K.	1.9	0.8	0.5	1.2	xxx	9.0	6.0
8	E. H.	3.1	1.1	1.0	2.3	xx	11.8	4.9
9	G. D. G.	4.5	1.8	2.9	4.0	x	10.1	4.2
10	M. L.	3.6	1.2	2.0	2.9	xx	10.2	4.8
11	E. H.	1.4	0.5	0.8	1.2	xxx	7.2	5.0
12	B. G.	4.2	2.2	2.6	3.2	xx	11.4	4.6
13	C. G.	1.8	0.9	0.5	1.1	xxx	11.2	5.6
14	L. F. K.	4.4	2.6	2.4	3.9	x	11.6	4.5
15	H. A.	4.0	2.2	2.0	3.5	xx	10.0	4.7
16	M. F. S.	1.8	0.7	0.9	1.2	xxx	10.0	5.7
17	F. P.	4.9	1.3	3.0	3.9	x	9.8	4.5
18	M. B. B.	2.0	0.7	1.2	1.6	xxx	9.6	5.5
19	F. D.	3.1	1.1	1.9	2.4	xx	8.3	5.0
20	E. C. D.	4.5	1.6	2.7	3.6	xx	9.3	4.6
	Average						10.2	4.89

The criteria for the diagnosis of parathyroid insufficiency therefore became: (1) Spontaneous attacks of tonic contractions in extremities ("accoucheur hand," carpopedal spasm); (2) of the facial muscles—trismus; (3) of the laryngeal muscles—laryngeal spasm; (4) mechanical hyperexcitability of the peripheral nerves—

the Trousseau, Chvostek and Poole phenomena, also called the arm and leg phenomena.

The Trousseau phenomenon and the Chvostek phenomenon were both described by clinicians in the period before their relations to the parathyroid glands was understood or guessed, the one in 1864 and the other in 1878.

TABLE II.—COMPARISON OF ELECTRICAL IRRITABILITY OF ULNAR NERVE—CHVOSTEK REACTION, NORMAL BLOOD CALCIUM AND NORMAL BLOOD PHOSPHATE—IN NONPARATHYROID CASES.

	Name.	K O C	K C C	A O C	A C C	Chvostek	Blood calcium.	Blood phosphate.
1	E. S.	6.2	2.4	3.6	4.4	0	11.6	3.0
2	B.	5.5	2.2	3.5	4.4	0	10.1	3.6
3	W. L.	5.0	1.8	3.0	4.1	0	9.8	3.6
4	R. H.	6.9	2.5	4.8	5.8	0	11.9	3.5
5	N.	6.0	2.1	5.1	5.2	0	11.3	2.6
6	E. S.	5.0	1.9	2.1	2.8	0	10.8	4.4
7	A. S.	6.5	2.8	3.9	4.8	0	11.2	4.1
8	F. O. S.	5.1	1.9	3.0	4.4	0	9.6	3.7
9	F. Mc.	4.9	2.0	2.9	4.1	0	10.1	4.1
10	J. S.	5.0	1.8	2.9	4.4	0	10.8	4.0
11	Th. T.	4.8	1.8	2.1	4.0	0	9.1	4.2
12	W. M. H.	5.8	2.2	2.2	3.8	0	11.9	4.2
13	J. J.	5.4	2.3	3.4	4.2	0	11.8	3.5
14	G. M.	5.0	2.5	3.2	4.0	0	11.8	3.6
15	H. D. K.	5.2	2.9	3.5	4.2	0	9.9	3.2
16	Ch. H.	5.5	2.5	3.6	4.4	0	10.0	3.8
17	A. H. N.	5.2	2.3	3.2	4.0	0	10.8	3.9
18	G. G.	6.0	2.8	2.9	3.9	0	10.1	4.2
19	M. J. G.	6.0	2.5	3.0	4.2	0	10.2	4.1
20	M. U.	5.1	2.2	3.0	4.4	0	10.6	3.9
21	E. A.	7.0	3.1	3.2	4.9	0	12.0	4.0
22	H. G.	5.4	2.6	3.0	4.1	0	10.9	4.1
23	W. S.	5.1	2.0	3.4	4.3	0	11.1	3.0
24	M. B.	5.3	1.9	3.1	4.0	0	10.1	3.9
25	B. G.	5.0	2.2	2.9	4.0	0	9.8	4.0
26	J. R.	6.9	3.2	4.1	5.2	0	12.0	3.9
27	H. G. S.	5.2	3.1	3.0	4.1	0	11.0	4.5
28	H. D.	6.5	2.6	3.8	4.9	0	12.0	3.8
29	K. S.	5.8	2.3	3.5	4.6	0	10.8	3.2
30	J. L. L.	5.0	2.2	2.9	4.0	0	10.2	4.1
31	C. C.	5.8	2.6	3.0	4.1	0	10.8	4.3
32	E. H. D.	5.0	2.1	2.8	3.9	0	9.7	4.3
33	A. D. L.	5.1	2.4	3.2	4.1	0	10.4	3.5
34	I. F.	5.5	1.8	2.9	3.6	0	9.8	4.1
35	L. B. D.	5.8	2.1	2.5	3.9	0	10.0	4.3
36	L. A.	5.0	2.2	2.2	3.5	0	9.8	4.3
37	M. W.	5.9	2.5	2.1	...	0	11.0	4.1
	Average						10.9	3.96

The Trousseau phenomenon is produced by the application of a ligature firmly about the upper arm. The pressure should be

sufficient to prevent perception of the pulse, and the palm should be stroked. It consists in the assumption of the obstetrical hand after three to five minutes.

The Chvostek phenomenon is the response to mechanical stimulation (tapping or pinching) of the facial nerve at its point of emergence from the parotid gland as the *pes anserinus*. There results a contraction of some or all of the muscles of the same side of the face; that is, there may be only a twitch of the angle of the mouth, or a twitch with a contraction of the nostril of the same side, or there may be these and a momentary twitch of the eye at the same time. These are classified as Chvostek X, XX or XXX.

The arm and leg phenomena were first described by Ferenczi in 1904 and by Poole in 1906. They consist in the production of carpopedal spasm upon hyperabduction of the arm and hyperflexion of the thigh with the knee extended.

The fifth criterion of parathyroid insufficiency is the measurement of the increased nerve irritability by a determination of the amount of galvanic stimulation necessary to act as a stimulus. Because first applied by Erb, this has become known as the Erb phenomenon. Von Pirquet standardized a procedure for its determination in 1907, and made a detailed study of the facts obtained. (One large electrode properly moistened and protected is placed upon the abdomen; the other stimulating small electrode is placed upon the nerve, ulnar, median or peroneal, to be stimulated. A quantitative measure of the degree of parathyroid insufficiency can thus be obtained.) For practical purposes a cathodal opening contraction, KOC, with a current of less than 5 ma. demonstrates increased galvanic excitability. When such KOC hyperexcitability cannot be elicited, the occurrence of a cathodal closing tetanus contraction, KCTe, with less than 5 ma. proves the existence of hyperirritability, although of a milder degree than that producing a KOC with less than 5 ma.

Clinically, certain manifestations may be looked for in chronic tetany or in tetanoid or hypoparathyroid conditions. The first is hypoplasia or defects of the enamel of the teeth. These manifest themselves as transverse grooves or furrows in the enamel, or as minute excavations in the enamel or as chalky looking spots in the enamel, which contrast with the appearance of the rest of the enamel. In children who have had a series of attacks of tetany these defects will appear as several parallel areas, each corresponding to a period of parathyroid insufficiency. Erdheim in his classic experiments on rats described a similar appearance of their teeth. Similar trophic disturbances of the nails may occur. A third trophic disturbance to look for is that known as perinuclear cataract. The dilated pupils reveal the perinuclear cataract when examined with a strong lens. Disturbances in growth of the hair may also be found quite frequently when looked for.

Chemically, two facts have been established concerning the blood and metabolism in parathyroid insufficiency. One is the loss of calcium from the tissues, a negative calcium balance being established while there is a definite lowering of the blood calcium. The other is the decrease in the phosphate content of the urine, accompanied by a retention of phosphate in the tissue in experimental tetany. Greenwald has recently reëmphasized this. In 1923 Salvesen, of Christiana, showed that in "latent tetany," that is, in parathyroidectomized animals kept alive by the administration of calcium salts, the calcium content of the blood is below normal and the inorganic phosphate is above normal. He made no observations on the electrical irritability of the nerves. In clinical latent tetany, however, or in individuals presenting other stigmata of chronic parathyroid insufficiency, I am aware of no studies in which the calcium content of the blood, the phosphate content and the electrical irritability of the nerves have been compared.

In studying individuals who presented themselves in office practice during the past year twenty patients were found who presented clinical stigmata of parathyroid insufficiency, increased electrical irritability and a positive Chvostek reaction. Chemically, however, they differed from typical examples in that the blood calcium fell within the average limit, or even above, of 9 to 11 mg. per 100 cc. But they, all except one, presented a blood phosphate definitely above the normal average, which lies between 3 and 4.5 mg. per 100 cc. A list follows showing the various data. The results have been compared with a series of individuals who showed no stigmata of parathyroid insufficiency. The conclusion may be drawn that at least in the milder forms of chronic parathyroid insufficiency, there need be no decrease in the calcium content of the blood, but there is always an increase in the inorganic phosphate of the blood.

Conclusions. These criteria therefore may be used in the diagnosis of chronic parathyroid insufficiency and in gauging the effect of treatment:

1. Dystrophies of the hair, nails, teeth and skin.
2. Mechanical hyperexcitability of the nerves: Trousseau and Chvostek phenomena.
3. Electrical hyperirritability of the peripheral nerves.
4. Diminished calcium content of the blood — negative calcium balance.
5. Decreased phosphate content of the urine — phosphate retention in tissues, increased phosphate content of the blood.

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PRIMARY CARCINOMA OF THE LUNG.

A Clinical and Pathologic Study from the Cook County Hospital, with a Report of 21 Necropsies and 3 Biopsies.

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Introduction. In reviewing the literature on primary carcinoma of the lung, one is struck by the fact that in spite of the marked increase in necropsy reports in the last few years, most writers still persist in calling the condition a rare one. It seems to us that Barron[1] struck the keynote when he wrote, "It has almost been a tradition that carcinoma of the lung is an extremely rare disease, of negligible clinical importance, and that its antemortem diagnosis is practically impossible." We wish to emphasize Barron's use of the word "tradition," and make an appeal for the elimination of the use of the word, and face the facts as they are, namely, that primary carcinoma of the lung is not a rare condition, and that it can be diagnosed antemortem.

Adler,[2] in 1912, stated that primary malignant neoplasms of the lung are among the rarest forms of disease, while Hampeln,[3] in 1919, wrote that since 1895 the idea of the rarity and inability to diagnose primary tumors of the lung has been gradually changed. Packard,[4] in 1917, wrote that medical literature has been extensively enriched by published reports on cancer of the lung. Whether this wealth of material is due to a greater efficiency in diagnosis or whether pulmonary malignancies are on the increase remains at the present a much mooted question.

Since 1917 the literature has contained an unusually large number of case reports, the majority of which are authentic, as they are accompanied by necropsy reports.

Our interest in this subject was aroused by having 3 cases of malignant tumors of the chest within a period of a few weeks in one medical ward at the Cook County Hospital. This report, therefore, includes 21 cases of primary carcinoma of the lung with necropsy reports and 3 cases with biopsies. This includes all necropsy reports from January, 1917, to September, 1924. We do not wish to review the historical side of this subject, but would refer the reader interested in it to Moise[5] and Ewing.[6]

Statistics. It is fortunate that many careful necropsy reports have been made on this subject. Wolf,[7] in 1895, reported 45 cases of primary cancer of the lung in 20,116 necropsies (0.223 per cent) performed at the Dresden Hospital from 1852 to 1894. Reinhardt,[8] in 1878, reported 5 cases among 8716 autopsies from the City Hospital of Dresden. Fuchs[9] reported 0.065 per cent in a series of 12,307 necropsies from the Pathological Institute of Munich, from 1854 to 1885. Krause cites Hesse as having found 99 cases in 63,088 necropsies.[10] Passler[11] reported 16 cases (0.183 per cent) of pulmonary carcinoma in 9246 postmortems in the Pathological Institute of Breslau. Lavrinovitch,[12] in 1915, reported 61 cases in 16,407 necropsies. Von Wiczkowski,[13] in 1913, reported 126 cases in 58,497 necropsies (0.21 per cent). Rolleston and Trevor,[14] between 1890 and 1902, reported 6 sarcomas and only 2 carcinomas in 3983 necropsies at the St. George's Hospital (0.05 per cent). Oerstrom[15] gave the percentage as 0.31 in 10,272 autopsies at the Charité Pathological Institute in Berlin from 1900 to 1907. Briese,[16] in a report from the Pathologic and Hygienic Institute of Chemnitz in 12,971 cases found 60 (0.46 per cent) of primary tumors of the lung. Cotton[17] reported 29 cases from the Cantonal Hospital in Geneva from 1900 to 1920. Weller,[18] in 1913, reported 0.3 per cent in 11,093 autopsies. Symmers[19] reported 5 cases from the Pathological Laboratory of the Bellevue Hospital from 1907 to 1919, while from July, 1919, to December, 1920, there were 8 cases. Knierim,[20] in 1909, reported 66 cases of bronchial carcinoma, 7 acanthomas and 2 alveolar tumors. Fishberg[21] reported 33 cases from the Montefiore Hospital from 1915 to 1920. Scott and Foreman[22] reported 3 cases in 302 autopsies. Barron[1] reported 13 cases in 4362 autopsies from the Department of Pathology of the University of Minnesota from 1899 to June, 1921 (0.29 per cent), and further states that from January, 1919, to June, 1921, there were 1003 necropsies, which included 9 cases of primary carcinoma of the lung (0.9 per cent). Moise[5] reported 5 cases in 375 consecutive autopsies (1.38 per cent). Playfair and Wakeley,[23] in a study of 3183 autopsies at the King's Hospital were able to find only 4 clearly established cases in the records from 1901 to 1923. This

is a surprisingly small number, and taken with Rolleston and Trevor's report makes one think that carcinoma of the lung in England is a very rare condition. Maclachlan,[24] in 1923, stated that during the past year he has seen four times as many cases as had been observed in the previous eleven years. He reports 5 cases in 375 autopsies.

From January, 1917, to September, 1924, 3659 autopsies were performed at the Cook County Hospital, and of this series there were 21 cases of primary carcinoma of the lung, a percentage of 0.57 of all necropsies.

Statistics by various authors indicate an incidence of 0.15 per cent or more of all autopsies, about 1 per cent of all carcinomas and 2 per cent of all deaths from pulmonary disease.

Etiology. In discussing the etiology of primary carcinoma of the lung one is just as much at a loss as with carcinoma elsewhere, although in recent years numerous authors, especially Moise and Barron, have suggested that the increase in carcinoma of the lung may be referable to postinfluenzal lesions. These writers refer to the work of Winternitz and his associates,[25] in 1920, in which they then suggested the probability of an increase in carcinoma of the lung on the basis of postinfluenzal lung changes. Moise[5] further states that even though no clinical history of influenzal infection is present, still it is quite conceivable to attribute the increase of carcinoma of the lung to postinfluenzal lesions. In only 1 case here reported was a history of influenza elicited.

Wohl[26] states that the recent wave of pulmonary infections, such as streptococcic bronchopneumonia and influenza, constitutes an important factor in the formation of pulmonary neoplasms. From the above, though the evidence is far from conclusive, it would seem more probable that acute inflammatory processes rather than chronic irritations play a strong role in enhancing the formation of neoplasms of the lung.

Most authors, including Ewing, have given tuberculosis as the chief etiologic factor; yet in only 1 of our cases was any evidence of pulmonary tuberculosis found. This to us seems worthy of mention, because of the fact that more than one-half of the autopsies at the Cook County Hospital are performed on colored patients, and the ravages of tuberculosis among the colored race are well known. The fact that only 2 of the 24 cases here reported occurred in colored patients appears to be significant. In the past the greatest emphasis has been placed on the association of tuberculosis with carcinoma, although it seems to us with very little ground, and now the recent increase in primary lung tumors would further tend to support Rokitansky's dictum. Carmen[10] stated that tuberculosis and carcinoma of the lung may exceptionally coëxist, although in 17 autopsies no tuberculosis was observed.

In 1878 Harting and Hesse described the Schneeberg carcinoma

of the lung, and stated that a lymphosarcoma of the bronchial lymph nodes or an endothelial sarcoma was responsible for 79 per cent of all the deaths among the miners of the Schneeberg district of Saxony. However, as autopsies are rare in this district, Arnstein suggested that it is possible that many cases were tuberculosis or pneumoconiosis.[27] That Arnstein's contentions were partly true may be surmised from a recent report by Saupe,[28] who stated that in the majority of the cases pneumoconiosis is found in the miners of Schneeberg, and sometimes there is an associated malignant tumor of the lung; while tuberculosis apparently plays a less important role. Saupe, therefore, believes that miners' disease in Schneeberg is caused partly by pneumoconiosis and partly by a true malignant tumor of the lung. Males are definitely more predisposed than females, the ratio being given as 3 to 1. In this series only 2 cases occurred in females. In Adler's series of 374 cases 113 occurred in individuals between fifty and sixty years of age. Seven in our series occurred between the above ages, while 6 occurred between sixty and seventy years. Our youngest patient was twenty-nine years of age, although primary tumors have been reported in children. The white race is definitely more predisposed than is the colored race. Heredity has not been shown to be of any importance.

TABLE I.—AGE INCIDENCE.

Years.	No. of cases.	Years.	No. of cases.
20 to 30	1	50 to 60	7
30 to 40	5	60 to 70	6
40 to 50	5		

Various authors have tried to associate the production of lung tumors with the after effects of gassing during the late war. Up to the present time no definite conclusions have been reached, although Haggard[29] states that chronic after-effects of gassing may result if the damage is severe enough to produce chronic inflammatory changes. These, for the most part, take the form of chronic bronchitis, pulmonary fibrosis and occasionally abscess formation.

Pathology. In considering the etiology of this condition from a pathologic viewpoint, it is natural that tuberculosis, a very frequent pulmonary condition, should be considered as important. Other pulmonary inflammations, such as bronchiectasis, influenza, chronic interstitial pneumonia and chronic bronchitis are also believed to be of etiologic significance. Ewing states that the chief etiologic factor is tuberculosis, and mentions the cellular overgrowth and alterations of bronchial and pulmonary epithelium found in the old sclerosis, atelectasis and reparative lesions of tuberculosis. Wolf[7] is stated to have found tuberculosis in 13 of his series of 31 cases of carcinoma of the lung, several of which showed active miliary dissemination, suggesting that the malignant process may light up

a latent tuberculosis. The association of pulmonary carcinoma with tuberculosis has been repeatedly cited in literature, although series have appeared in which the coexistence of the two was praccally absent. Rokitansky's old dictum that the presence of tuberculosis practically precludes carcinoma appears to be contrary to the generally accepted views concerning pulmonary carcinoma. The findings in the series of cases here reported would tend to sustain him, as in only 2 of the autopsies was any tuberculosis found, and only 1 of which was pulmonary in location.

Kaufmann[37] mentions the fact that pulmonary cancer develops in the walls of bronchiectatic cavities as well as those of tuberculous nature. Three of our cases were associated with bronchiectasis, but we agree with Barron,[1] that this is more often the result rather than the cause. Stenosis of the bronchi in consequence of the growth itself or of the inflammatory changes associated with it may easily give rise to bronchiectatic dilatation with cavitation.

Reports suggesting an increasing incidence of pulmonary carcinoma in the past three or four years have appeared repeatedly in the literature and our series seems to agree with these observations. The great influenza epidemic with the resultant acute inflammatory insults to the respiratory system has been held responsible for the decided increase in the number of cases reported. Winternitz, Wasson and McNamara,[25] in their study of the pathology of influenza, have pointed out the frequent destruction of the basement membrane of the epithelial structures, and they suggested in 1920 the probability of an increase of lung tumors on the basis of the epithelial overgrowth observed.

Adler,[2] in a study of 374 collected cases, found 188 of the cancers in the right lung and 157 in the left lung. Weller,[18] in an analysis of 89 cases, found the right and left sides affected with equal frequency. Barron[1] stated that the right lung is affected more often than the left, and the upper lobe more frequently than the lower. In Adler's series the most extensive change was in the upper lobe in 91 cases, in the hilar region in 90 and in the lower lobe in 75. Practically an entire lung was affected in 48 cases, and apical involvement was found in 16.

In our series the left side was affected in 12 cases, the right side in 5 and both sides in 3. The most extensive changes occurred in the upper lobe in 11 cases, the lower lobe in 5 and the whole lung was fairly uniformly affected in 4. In 17 the relation to the hilus was marked. Apical involvement was present in 5 cases, occurring as part of a disseminated invasion of the entire lobe or lung involved. In 8 instances the gross findings suggested an origin from a primary bronchus, 5 from a secondary bronchus and in 6 cases the origin was not grossly determinable. In one of the tumors the primary nodule appeared to be located in the lower part of the trachea. Ulceration of the bronchial mucosa at the site of the

growth occurred in 3 instances, while narrowing of the lumen of the bronchus involved was found in 7 cases, due either from pressure without or to actual plugging of the bronchus by the growth.

The gross appearances of these tumors present many variations, depending upon the stage at which the neoplasm is observed, and also upon the mode of growth. Adler makes note of the lack of uniformity of the gross appearances. The following forms have been described: (1) Infiltrating, (2) multiple nodular, (3) solitary nodular, (4) miliary and (5) mixed.

Kaufmann[37] describes an infiltrating form resembling a caseous pneumonic involvement of an entire lobe. Aschoff[38] describes similar grayish or yellowish masses with poorly defined limits and of very uncertain origin. Moise[5] notes that the infiltrating type is the usual one seen in advanced stages. McMahon and Carmen[39] describe a form which arises from a large bronchus with penetration of the wall and invasion of the lung tissues along the bronchi, bronchioles, alveolar walls and air spaces. Massive involvement of a single lobe or lung may occur by way of the lymphatics, blood-vessels, direct extension, gravity and aspiration. Adler mentions another type of infiltrating tumor starting from a smaller bronchus or bronchiole affecting only a portion of one lobe with a very dense growth.

Gross characteristics conforming with the above description were encountered in 11 of our cases. Of these 1 was considered alveolar and 10 bronchiogenic in origin. The growth was limited to a lobe in 8 instances, while in 3 all the lobes of a lung were involved. In all of these the tumor had evidently arisen in the hilus and extension was occurring peripherally to involve the parenchyma of the lung. No apical involvement was noted in any of the above cases, although invasive characteristics were more or less pronounced in all of them. Degenerative changes were noted in all but 3.

A solitary nodule, occurring very rarely, is described deeply buried in the tissues of a lobe. This may be surrounded by a few minute miliary nodules. This type produces slight symptoms or none, and is said to occur very rarely. Two such tumors were found in our collection. In 1 of these there was a small circumscribed tumor mass about 3 cm. in diameter buried deeply in the substance of the right upper lobe. The other existed as a solitary nodule in the hilum of the left lower lobe. Neither of these were invasive in character, nor did they show degenerative changes. Following histologic study one was considered bronchiogenic in origin and the other a questionable bronchiogenic type.

A multiple nodular type, involvement at first being limited to one portion of the lung, is described by Adler. The nodules may be very numerous, with marked variation in size and with sharply defined boundaries. There may be a rather large circumscribed tumor mass in the center of the lobe, surrounded by nodular foci,

which may eventually involve other lobes. This type occurred twice in our series. In the first there were many nodules distributed diffusely throughout both lungs, while in the second there was widespread involvement of only the right lung. Narrowing of the lumina of the adjacent bronchi occurred in both cases, while degenerative changes were noted in the nodules of one.

A miliary form is described, resembling tuberculosis, with symmetrical and diffuse involvement throughout both lungs, the tumor being slightly larger than tubercles. The nodules are more or less translucent white in color. Involvement occurs along the course of the lymphatic channels, indicating an early lymphatic invasion of the lung. This type of growth was met with only once in our series. This, however, did not conform with the accepted picture, as only the left lung was involved. The nodules were very small, some being 1 to 2 mm. in diameter. The distribution throughout the affected lung was very diffuse; the periphery, central portions, apex and the base were equally involved.

The mixed type presents a combination of infiltrative and miliary or nodular forms in the same case. In addition to an infiltrating mass in one or more lobes, the remainder of the lung is diffusely studded with nodules varying in size and number. Four of our cases corresponded grossly to the above description.

Histologically pulmonary carcinoma shows a rather varied picture. The following classification as to cell type has been used: (1) Cylindrical-cell carcinoma, (2) squamous-cell carcinoma, and (3) mixed-cell type.

Cylindrical-cell carcinoma has been subdivided into numerous groups on the basis of histologic structure. Adenocarcinoma is reputed to be the most common, the structure presenting a glandular appearance. Carcinoma simplex, composed largely of solid masses of tumor cells is supposed to arise from bronchial epithelium or from mucous glands. A scirrhous type occurs characterized by a slow growth and enormous amounts of connective-tissue proliferation with relatively few tumor cells. Alveolar carcinoma is characterized by solid masses of pleomorphic cells occupying spaces resembling lung alveoli. A medullary carcinoma has been described, resembling sarcoma; which is composed of compact, small pleomorphic cells having little cytoplasm. Colloid or gelatinous carcinoma derives its name from the rich colloid content.

Squamous-cell carcinoma is believed to occur as a result of metaplasia of cuboidal epithelial cells. Another theory accounts for its occurrence on the basis of embryonic displacement of islands of squamous cells. Most of these tumors are believed to originate in the scars and walls of tuberculous cavities.

A mixed type has been encountered in which there are several of the above types of cells and structures in the different portions of the same growth.

In 55 cases reviewed by Weller,[18] 45 were alveolar, acinar or adenomatous, 5 were medullary, 3 scirrhous and 2 simplex. We are unable to review the histologic structures of this series of tumors, because detailed microscopic records are not available in many of the cases.

Attempts to establish the histogenesis of cancer of the lung have naturally been directed at the three types of epithelial cells which occur in the pulmonary system. However, it is admitted that it is impossible to determine the histogenesis of the majority of the tumors, because of the uncertainty associated with the morphology of the cells. It is essential that the cases be studied during the early stages of the disease. Other difficulties result from the modification of the tumor cells as a result of inflammatory processes to which lung tissue is susceptible. In addition the secretory cells of the mucous glands, the pavement cells of the alveoli and the bronchial epithelium are closely related morphologically, the first two being merely modified columnar cells which line the bronchi.

The ordinary criteria by which many tumors have been classified histogenetically are inaccurate, since some of the authors have attributed alveolar origin to tumors composed of squamous cells, merely because they happen to resemble the flat cells lining the alveoli. Since bronchial epithelial cells, as well as mucous gland epithelium, may secrete mucus, it is inaccurate to trace the origin of tumors to the latter, simply because the neoplasm presents an abundant mucoid secretion.

Under ordinary circumstances, therefore, it is obviously impossible to definitely classify a given pulmonary carcinoma according to its histogenesis, and yet this is the most prevalent method of classification. Ewing[6] discusses these tumors under headings of those arising from: (*a*) Bronchial epithelium, (*b*) alveolar epithelium and (*c*) bronchial mucous glands. He also states that to a considerable extent these types are distinguished by gross anatomic features and by certain clinical ones. He modifies this by saying that it is difficult to separate all advanced cases, especially the more malignant types; for the specific features belong chiefly to the earlier stages. In discussing the histogenesis, he states that there are comparatively few opportunities to trace the origin of this type of neoplasm. He regards conclusions as to histogenesis reasonably certain upon the evidence of histologic structure, gross anatomy and clinical history.

We believe that a histogenetic classification of these tumors is not acceptable under ordinary circumstances because the histologic studies are confusing and inaccurate, the gross anatomic findings are not characteristic and, finally, the clinical history of little or no value. Our series of cases were examined by competent and well-trained pathologists, who classified each tumor under one of the above three headings. Sixteen were considered to be of bron-

chogenic origin, 2 alveolar, 1 of mucous gland origin and 2 questionable. In reading the gross reports it is evident that most of these tumors were too far advanced to allow gross anatomic appearances to be of value. It is evident that classifying these neoplasms as arising from one or another type of epithelium admits great probability of error. It may be truthfully stated that many of the tumors reported in the literature as bronchiogenic, alveolar, and so forth, are subject to the same inaccuracy. In submitting our version of the histogenesis of our tumors we desire to demonstrate only the usual conclusions reached, and do not present these as accurate studies in histogenesis.

The consensus of opinion is that the majority of these tumors arise from the bronchial epithelium, and that only a few arise from the parenchymal or alveolar epithelium. Adler[2] states that a primary carcinoma of the lung is a bronchial carcinoma. Kaufmann,[37] on the other hand, believes that the origin is most frequently from the mucous glands.

Ewing describes carcinoma of the bronchial lining epithelium as producing extensive changes in the bronchial mucosa, advancing along the walls of the bronchi, septa and pleura, but seldom producing a diffuse tumor of the lung. The process usually begins at or below the bifurcation and extends toward the trachea above and the smaller bronchi below. The bronchi may be filled with papillary projections over a wide area invading the parenchyma and producing a thickening of the walls. Ewing quotes Chiari, Tillman and Peck in stating that the presence of very high cylindrical cells and their persistence in metastases indicate an origin from the bronchial mucosa.

Tumors arising from the mucous glands have been described as having quite characteristic gross and microscopic features. Limitation of the growth chiefly to the walls and submucosa of the bronchi, freedom from ulceration of the mucosa, narrowing rather than dilatation of the bronchi and an adenocarcinomatous or alveolar carcinomatous structure with cell groups resembling mucous glands, are features considered more or less characteristic of this type. The secretion of mucus, although occurring also in tumors arising from bronchial mucous lining, is a prominent feature of this type, and is strongly suggestive of mucous gland origin. However, the age of the growth, the rapidity of the same and secondary changes may result in marked variations from the typical structure and gross findings.

Ewing describes diffuse and nodular types of carcinoma arising from pulmonary alveoli. In the diffuse form an entire lobe or lung is uniformly consolidated, the lesion resembling the gray hepatization of croupous pneumonia or an organizing pneumonia. The structure of these tumors shows a filling of alveoli with cuboidal, cylindrical or flat cells, the vesicle walls being either preserved or

TABLE II.—VARIOUS METASTASES.

Case.	Lymph metastases.											Regional metastases.				Organic metastases.																		
	Axillary.	Mediastinal.	Periaortic.	Cervical.	Abdominal.	Iliac.	Femoral.	Perigastric.	Peripancreatic.	Periesophageal.	Peribiliary.	Lungs.	Pleuræ	Pericardium.	Bronchi.	Adrenals.	Liver.	Kidneys.	Bones.	Brain.	Cord.	Heart.	Appendix.	Skin.	Spleen.	Omentum.	Mesentery.	Pancreas.	Thyroid.	Tonsil.	Tongue.	Ileum.	Dura mater.	Peritoneum.
I . . .	. .	+	. .	+	. .	. .	. .	. .	. .	. .	. .	+	. .	. .	. .	+	+	+	+	+	. .	. .	. .	. .	+	+	+	+						
II . . .	. .	+	. .	+																														
III . . .	. .	+	+	. .	+	+	+	. .	. .	. .	. .	+	. .	. .	. .	+																		
IV . . .	. .	+	. .	. .	. .	. .	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	+	+	+	+														
V . . .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	. .	+	. .	. .	+	. .	. .	. .	. .	+												
VI . . .	. .	+	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	. .	. .	. .	+	. .	. .												
VII . . .	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	+	+	. .																			
VIII . . .	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	+	+	+	+	+																	
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XI . . .	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	. .	. .	. .	+	+																	
XII . . .	. .	+	+	. .	. .	. .	. .	. .	. .	. .	. .	+	+	+	. .	+	+	. .	+															
XIII . . .	. .	+	+	. .	. .	. .	. .	. .	+	. .	+	+	+	. .	. .	. .	+																	
XIV . . .	. .	. .	. .	. .	. .	. .	. .	+	. .	. .	. .	+	+	. .	. .	+	. .	+	+	+	. .	. .	. .	+	. .	. .	+	+						
XV* . . .	. .	. .	. .	+																														
XVI . . .	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	. .	. .	. .	. .	. .	+																
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XX . . .	. .	+	+																															
XXI . . .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	+	+	. .	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	+
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XXIII . . .	+	+	. .	+	. .	. .	. .	. .	. .	. .	. .	. .	+	+	. .	. .	+	+	+	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	. .	+	. .	+
XXIV* . . .	. .	. .	. .	+																														

* Biopsy.

TABLE III.—ASSOCIATED LESIONS.

Case.	Type.		Lungs.		Bronchi.		Pleura.			Pulmonary osteoarthropathy.	Tuberculosis.		Pathologic Fracture.	Mediastinitis.	Compression of sup. vena cava.
	Bronchogenic.	Alveolar.	Subinucous.	Compression atelectasis.	Pneumonia.	Hyperemia, hypostatic or passive.	Abscess.	Bronchitis. Chronic indurative.	Bronchitis. Suppurative.	Bronchiectasis. With cavitation and abscess.	Bronchiectasis. Without cavitation.	Pleura. Chronic. Obliterative.	Chronic. Focal.	Acute. Fibrinous.	Acute. Serosanguineofibrinous.	Hemothorax.	Hydrothorax.	Empyema.		Glandular.	Pulmonary.			
I	+	:	:	:	:	:	:	:	+	:	:	:	+	:	+	:	:	:	:	:	:	:	:	:
II	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
III	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
IV	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
V	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
VI	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
VII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
VIII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
*IX	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
X	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XI	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XIII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XIV	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
*XV	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XVI	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XVII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XVIII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XIX	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XX	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XXI	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XXII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
XXIII	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:
*XXIV	+	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:	:

* Biopsy.

obliterated by tumor growth or inflammatory changes. The nodular form presents in one or both lungs multiple tumor foci varying in size and showing necrotic areas. The structure of this type shows groups of slightly dilated air vesicles filled with papillary projections of cylindrical cells.

Authentic cases of alveolar origin are very rare. Passler,[11] in discussing the alveolar origin of tumors, stated that 47 of the 54 reported alveolar tumors or 8 per cent were apparently bronchial in origin.

The metastases of pulmonary carcinoma are widespread, only a few cases being reported without secondary growths. Due to the great vascularity of the organ and the abundant lymphatic channels, widespread dissemination by way of the blood stream and regional extension by way of the lymphatics frequently occurs. Of the 374 cases reported by Adler there was invasion of the bronchial nodes in 117; mediastinal in 45; tracheal, 26; cervical, 23; retroperitoneal, 23. The liver was invaded in 103 cases; pleura, 52; pericardium, 39; heart, 30; kidneys, 58; adrenals, 38; spleen, 18; brain, 53; bones, 47. Metastases were absent in 33 cases.

All of our cases showed metastases to the regional lymph nodes and distant organs. In only 3 of the 21 autopsies were metastases limited to the regional lymph nodes, the others showing involvement of distant organs as well.

The following groups of glands were involved: Tracheobronchial and mediastinal, 18; periaortic, 5; cervical, 6; abdominal, 3; iliac, 1; femoral, 1; axillary, 1; perigastric, 2; peripancreatic, 2; peribiliary, 2; periesophageal, 1. The following regional metastases were found: Lungs, 13; pleura, 8; pericardium, 7; mediastinal and cervical tissue, 5; trachea, 1. Metastatic deposits were found in the following organs: Liver, 12; adrenals, 5; kidneys, 8; bones, 8; brain, 5; heart, 1; appendix, 2; skin, 3; spleen, 2; omentum, 1; mesentery, 2; pancreas, 4; thyroid, 1; tonsil, 1; tongue, 1; ileum, 2; dura mater, 1; peritoneum, 2. Metastases occurred in the following bones: Ribs, 5; calvarium, 2; vertebra, 1; zygoma, 1; ilium, 2; neck of the femur, 1; occipital bones, 1; sphenoid, 1. Three instances of pathologic fracture were encountered.

Consideration of the associated pathology is important because these secondary complications frequently alter the clinical and pathologic picture. Adler found pleural fluid of varying amounts in 46 of 374 cases. Cavities small or large, single or multiple, in the carcinomatous tissue were found in 60 cases. Bronchiectasis was found in 28 instances. Only 19 were associated with tuberculosis. Atelectasis from bronchial obstruction or compression and pneumonias of various types were mentioned in a few cases.

Dana and McIntosh[40] found 37 instances in the literature of obstruction of the superior vena cava by carcinoma of the lung. In 14 of these cases the carcinoma was primary in a bronchus. In

only 6 cases was the diagnosis verified by autopsy. Two of our series of cases showed superior vena cava obstruction at postmortem examination, both of which occurred in tumors arising from the right side. One of these cases presented edema of the neck, thorax and upper extremities and also varices of the veins of the neck and scapular region. In 1 case a tumor thrombus was found in the left pulmonary vein.

Compression atelectasis of the lungs occurred in 7 of the necropsies and pneumonias of various types were noted in 9. Pulmonary abscess was recorded in 5 of the autopsies, and hypostatic and passive hyperemia in a similar number. Bronchiectasis with cavition was seen in 3 cases, with 2 of which pulmonary osteoarthropathy was noted. Chronic bronchitis (indurative, 1; suppurative, 3) was encountered in 4 cases. Pleuritis occurred in a relatively large number of cases, the following forms being found: Chronic obliterative, 8; focal fibrous, 4; acute fibrinous, 3; acute serosanguineofibrinous, 3; suppurative, 1. Hemothorax was seen in only 3 cases, and hydrothorax in 2. Contrary to the generally accepted views, only 2 cases of healed tuberculosis were recorded, 1 pulmonary and 1 glandular. Emaciation was very prominent in 6 cases.

Symptoms. There are no pathognomonic symptoms of carcinoma of the lung; yet, the disease presents, as a rule, symptoms which should lead one to suspect its presence. Symptoms may vary greatly, in some cases being only pulmonary in character, in others consisting only of metastatic phenomena, while in others symptoms of a localized tumor are found, in others symptoms only of a pleural effusion are found and, finally, cases are seen in which no clinical phenomena are present.

In the series of cases here reported the most common symptoms in order of frequency were weakness, cough, expectoration, pain in the chest and dyspnea. Other symptoms noted were loss of weight, fever, night sweats and hemoptysis. Pain in the chest, which is frequently an early symptom, is usually of insidious onset, unilateral and of a dull, aching nature, although at times it may be sharp and stabbing. At times the pain is referred down the arm on the same side or is localized in one of the shoulder joints, possibly from referred pleural irritation. Fishberg and Steinbach lay great stress on the presence of pain in the chest as a great help in differentiating carcinoma from tuberculosis.

The cough has nothing characteristic. It usually is accompanied with some expectoration, which consists of yellowish mucus. In regard to the black currant jelly sputum upon which so much stress has been placed, nothing definite can be said, except that it is absent in more cases than it is present. In only 1 case in this series was a prune juice sputum observed.

Dyspnea is a symptom which may be present to only a slight

extent or may become orthopneic in character, or at times may resemble the dyspnea observed in bronchial asthma.

Weakness was a prominent symptom in all of the cases in this series, and was complained of by all as a feeling of excessive tiredness and gradual loss of strength.

Hemoptysis was noted only in 5 cases, although Fishberg states that in one-half of his cases hemoptysis was an early symptom.

A symptom concerning which there has been a great deal of discussion is fever. Weller emphasized the diagnostic importance of the absence of fever and night sweats, while on the other hand Hamman[30] stated that tumors of the lung are nearly always accompanied by fever, more commonly high and continuous. In regard to this point, we wish to state that it was the continuous absence of fever in 3 cases which led us to suspect carcinoma of the lung and which helped in finally diagnosing this condition. In 2 cases of these series the temperature was high and continuous, in 1 reaching 103° F., while in another case the temperature was pyemic in character. In most of the cases only a slight and occasional rise in temperature was noted. The presence or absence of fever will, of course, depend a great deal upon whether there is secondary infection in the tumor or not. From the above it would seem that Weller's statement in regard to fever was more nearly correct.

Loss of weight was present in all of the cases, and in most instances was quite marked, varying from 15 to 75 pounds, in a period of two to three months. As far as the pulse rate is concerned, nothing definite was noted, some cases showing a rapid pulse rate, while most of the cases showed no increase.

The physical findings which are most prominent are an area of marked circumscribed dulness with diminished or absent breath sounds, with diminished vocal and tactile fremitus and no rales. In cases in which the growth does not completely compress a bronchus one may get bronchial breath sounds, which have been called "cornage." This was first described by Behier. In regard to pleural effusion, Hamman[30] states that the pleura is commonly involved in tumor of the lung, and that pleural effusion is one of the chief symptoms. Bridges and Moser[31] state that all types of lung cancer produce pleural involvement, and this generally early in the course of the disease. In only 8 of this series were there pleural metastases with pleural effusion. This would not bear out the above statements in regard to early pleural involvement. As most writers have stated, the fluid accompanying pulmonary neoplasms accumulates very rapidly and has a tendency to completely fill the chest. The character of the fluid may vary from serous to bloody or a purulent type. The presence of a bloody pleural exudate suggests to many the possibility of malignancy, although Horder[32] states that the commonest cause of blood-stained pleural effusion is not malignant disease, but tuberculosis. Cell counts

on the pleural fluid showed a preponderance of lymphocytes. Bridges and Moser[31] report 2 cases and Rusk and Randolph[33] 1 case in which carcinoma cells were found in the aspirated pleural fluid. In view of this finding, it would seem advisable to look for tumor particles more carefully in suspected cases.

The great majority of cases in this series showed a leukocytosis in the blood stream, varying from 9000 to 20,000. Packard,[4] in his 7 cases, reported a leukocytosis varying from 10,000 to 20,000.

In regard to blood pressure a point may be brought out of some value. We all know the tendency to hypotension in cases of tuberculosis. In this series of cases in only 1 was a blood pressure below 100, that is, systolic, recorded. The finding, therefore, of an increased or normal blood pressure in an individual in whom one is trying to differentiate tuberculosis from a lung tumor, may be a thread, though slight we realize, of help in substantiating the diagnosis of a lung tumor.

The course of carcinoma of the lung may vary from weeks to years. Cases of four years' duration have been reported by Adler and also by Pinchin.[34] Eight months was the longest duration of symptoms in this series.

Diagnosis. One of the prime requisites in diagnosing any disease entity is an appreciation, which should be constant, of the possible presence of that disease. If this were kept in mind we are quite certain that diagnoses of carcinoma of the lung would be made much more frequently than they are. Moise[5] states that lung tumors are only rarely diagnosed antemortem, and yet, at the Cook County Hospital, where the majority of diagnoses are made by the internes on the staff, 8 cases of this series of 24 (33.3 per cent) were correctly diagnosed antemortem. Fishberg and Steinbach,[21] in their series of cases were able to obtain a much more enviable record of antemortem diagnoses.

Fishberg and Steinbach[21] discuss the diagnosis of lung tumors in such a masterly fashion that we take it upon ourselves to quote freely from their article. They state that nearly all patients with malignant growths of the chest cough and expectorate sputum. It is important to think of a pulmonary neoplasm when a patient in the cancer age, showing no symptoms of cardiac, renal or arterial disease, begins to cough and is short winded. In patients who have passed middle age pain in the chest with or without pleural effusion is suggestive.

In a patient, therefore, who is of middle age or past, and who has unilateral findings of an area of dulness or flatness, associated with decreased or absent breath sounds or amphoric breath sounds; if in addition that patient has pain in the chest, with or without dyspnea, then one should strongly suspect a lung tumor. Rales appear rather late in neoplastic growths.

TABLE IV.—SYMPTOMS.

Case.	Sex.	Race.	Age.	Duration symptoms.	Pain in chest.	Cough.	Expectoration.	Hemoptysis.	Cyanosis.	Dyspnea.	Weakness.	Loss of weight.	Night sweats.	Rise in temperature.
1	M.	W.	29	?	+	+	+	O	O	O	+	+	+	+
2	M.	W.	64	4 months	O	O	O	O	O	O	+	+	O	O
3	M.	W.	45	6 months	+	+	O	O	+	+	+	+	O	+
4	M.	W.	45	2 months	+	+	+	O	O	O	+	+	O	O
5	M.	W.	65	3 months	O	O	O	O	O	O	+	+	O	O
6	M.	W.	52	4 months	+	+	+	+	O	O	+	+	O	O
7	F.	W.	69	4 months	O	+	O	O	O	+	O	+	O	O
8	M.	W.	65	2 months	O	+	+	O	O	O	+	+	O	+
9	M.	W.	42	4 months	+	O	O	O	O	O	+	+	O	O
10	M.	W.	39	2 months	+	+	+	O	O	O	+	+	O	O
11	M.	W.	57	1½ months	O	+	O	O	+	O	+	+	O	O
12	M.	W.	38	3 months	O	O	O	O	O	O	+	+	O	O
13	F.	Col.	70	5 weeks	O	+	+	O	O	O	+	+	O	O
14	M.	W.	50	1 month	+	+	+	O	O	O	+	+	O	O
15	M.	W.	57	5 weeks	+	+	O	O	+	O	+	+	O	O
16	M.	W.	60	?	O	+	+	+	O	O	+	+	O	+
17	M.	Col.	50	4 months	+	+	O	+	O	+	+	+	O	+
18	M.	W.	33	1½ months	+	+	+	O	+	+	+	+	O	+
19	M.	W.	44	2 months	+	+	+	+	O	+	+	+	O	+
20	M.	W.	31	2½ months	+	+	+	O	O	O	+	+	O	+
21	M.	W.	36	1½ months	O	+	+	O	O	O	+	+	O	O
22	M.	W.	45	8 months	O	+	+	O	O	O	+	+	O	O
23	M.	W.	55	4 months	O	+	O	O	O	O	+	+	O	O
24	M.	W.	55	2 months	+	+	+	+	O	O	O	+	+	+

Of late many men have been advocating bronchoscopy for the early diagnosis and treatment of lung tumors. Jackson and his associates[35] state that the bronchoscope has brought to the aid of the surgeon an absolute certainty of diagnosis not otherwise possible and, what is even more important, this absolutely certain diagnosis can be usually made at such an early stage that there is a chance to save the patient by lobectomy. They further state that deformity and fixity of the bronchi involved in the infiltrative process are very characteristic, and in the endobronchial cases either a mass, nodule, fungation or ulcer is present.

As further aids to the diagnosis one should remember biopsy examination of lymph nodes whenever they are accessible or examination of tumor particles removed by way of the bronchoscope. The sputum should be examined for tumor fragments or carcinoma cells, although this has proven very difficult and of little value. Examination of pleural exudates for carcinoma cells should also be made.

Many writers have stated that roentgenology offers little help in the diagnosis of lung neoplasms. On the other hand, about an equal number have stated that the Roentgen ray is of great help in making the diagnosis. Carmen[10] states that because of complicating factors, such as pleural effusion, interference with pulmonary circulation, atelectasis, bronchiectasis, tuberculosis and other pneumonic processes, there can be no constant Roentgen ray picture for carcinoma of the lung. However, he propounded Roentgen ray findings which should lead one to suspect carcinoma. In 3 of our cases the Roentgen ray made the diagnosis.

In the differential diagnosis one must first exclude tuberculosis. In this connection the persistent absence of tubercle bacilli in the sputum with marked symptoms and signs of pulmonary pathology should always arouse one's suspicion. Fishberg and Steinbach emphasize the importance of dyspnea and pain in the chest as hardly ever being seen in early phthisis. Conditions sometimes come up which are not pulmonary in nature, but which must be differentiated because of metastatic phenomena. Such conditions as tuberculous meningitis, brain tumor, chronic arthritis, gastrointestinal diseases and other diverse conditions occasionally must be considered. Pulmonary conditions to be differentiated include interlobar effusions, encysted empyemas, pneumoconiosis, bronchiectasis, lobar pneumonia and various mediastinal new growths.

Prognosis. As yet no definite treatment has been offered for carcinoma of the lung and, therefore, the prognosis remains quite hopeless. However, with the advent of bronchoscopy it is possible that some cases may receive early diagnosis and possible removal of the tumor.

Treatment. Measures relating to the treatment of this condition have as yet been unsuccessful. Surgical intervention is very

difficult, because the large majority of tumors start near the root of the lung, metastases occur rather early and, in addition, one is confronted with the presence of the large pulmonary vessels and the important mediastinal contents. Lenhartz, in attempting operative interference, was successful in 1 case out of 5, this case surviving eighteen months. Morriston Davies[23] reported a successful case of resection of a lobe of the lung for carcinoma of the lung. The recent report of Jackson and his associates[35] will surely stimulate the medical profession in having trained bronchoscopists make examinations of cases somewhat indefinite in diagnosis, and in this way help in the early recognition of lung neoplasms, with the resultant earlier institution of treatment.

Orton[36] reported a case of a pedunculated growth resembling a polyp just below the middle lobe bronchus on the right side. The growth was removed through the bronchoscope and proved to be a carcinoma of the papillary type. Green[36] also reported a case of a tumor in the left primary bronchus which was removed through the bronchoscope. The removal of tumors through the bronchoscope opens up a field, the results of which will be waited for in the future.

Deep Roentgen ray and radium treatment have been tried with little results.

Case Reports. CASE I.—C. C., a white male, aged twenty-nine years, was admitted to the hospital, October 3, 1921, complaining of cough, expectoration, pain in the chest and neck, night sweats and loss of weight. On physical examination the lungs showed dulness throughou t,particularly at the apices posteriorly. The breath sounds were prolonged, especially the expiratory phase. Many rales were heard throughout both lungs, more marked at the apices. During the patient's stay in the hospital he continued to grow weaker and began to complain of rigidity of the neck. There was a daily temperature fluctuating between 98.6° and 103° F. About a week before death the patient became delirious. The red blood count was 4,200,000; white blood count, 13,600, hemoglobin, 70 per cent. The urine was negative. Sputum was repeatedly negative for tubercle bacilli. Roentgen ray of the chest showed apical and peripheral shadows suggesting tuberculous involvement. A shadow suggesting encysted fluid was seen at the right cardiodiaphragmatic angle.

Necropsy. (November 15, 1921, by Dr. Moody.) The right lung does does not collapse and is everywhere solid. It weighs 1220 gm. On the surface there are nodules as large as 2.5 cm. in diameter, which are white and somewhat umbilicated, having a consistency of tumor tissue. Surfaces made by cutting the lower lobe showed one large tumor mass about 10 cm. in diameter composed of firm, white tissue. Throughout the remaining portions are many nodules which replace most of the lung tissue. The upper lobe is similarly studded. The left lung weighs 680 gm. and contains numerous tumor nodules.

Anatomic diagnosis: Primary carcinoma of the right lower lobe of the lung; metastatic carcinoma of the upper lobe of the right lung, both lobes of the left lung, brain, kidneys, eighth rib, liver, pancreas and spleen; metastatic carcinoma of the omentum, mesentery of the small bowel, adrenals, tracheobronchial and cervical lymph nodes; tumor infiltration of

the calvarium with perforation; mucopurulent tracheobronchitis, left focal fibrous pleuritis.

CASE II.—A. M., a white male, aged sixty-four years, was admitted to the hospital, October 16, 1923, complaining of loss of weight and asthenia. Physical examination revealed in the neck a large mass of discrete freely movable lymph glands in both supraclavicular fossæ. The lungs were negative. Abdomen showed fulness and tympany with slight tenderness and resistance in the epigastrium. There were no palpable masses or organs. Because of the suspicion of neoplastic disease in the gastro-intestinal tract an exploratory laparotomy was performed. This failed to reveal any lesions in the abdomen. The patient went steadily downhill, and died, October 27, of a terminal bronchopneumonia. The red blood count was 4,640,000; white blood count, 9700; hemoglobin, 80 per cent. The blood Wassermann was negative.

Necropsy. (Dr. Singer.) The right lung is distended and covered with fibrous tags. The parietal pleura is adherent over most of the upper lobe. Near the hilum of the right lung is a mass of tumor tissue about 3 cm. in diameter. This is firmly attached to the surrounding structures, and on section it is white and a milky juice can be expressed from it. The left lung was normal, except for a congestion of the lower lobe.

Anatomic diagnosis: Primary carcinoma of the right lung; tumor metastases to the tracheobronchial, cervical and subpleural nodes on the right side; obstructive volvulus of the sigmoid; recently amputated appendix; localized suppurative perityphilitis; bronchopneumonic foci of the right lower pulmonary lobe; submucous fibroma of the stomach; left focal fibrous pleuritis; obliterative right fibrous pleuritis.

CASE III.—F. B., a white male, aged forty-five years, was admitted to the hospital, October 13, 1920, with a complaint of pain in the chest and right scapular region, dyspnea and cough of about six months' duration. The onset of his illness was gradual with general malaise, cough and pain in the chest. Four weeks prior to entrance into the hospital he quit work because of severe and persistent pain in his chest, particularly over the sternal region. In the past five months he had lost 15 pounds. Examination of the patient was essentially negative, but in view of the slight afternoon rise in temperature with a rather rapid pulse and a history of cough and pain in the chest a diagnosis of pulmonary tuberculosis was made. On October 14 a Roentgen ray of the chest showed an upper right lobe fibrosis with evidence of a cavity in its center. This was interpreted as being either a collection of small bronchiectatic dilatations or a cavity *per se*. Repeated examinations of the sputum with and without antiformin failed to reveal any tubercle bacilli. The blood Wassermann test was negative. Nothing further developed until December 2, when the patient became cyanotic, dyspneic and had marked prominence of the veins on the right side of his neck and right arm. Physical findings were those of a solid tumor in the right apex causing pressure on the superior vena cava. Roentgen ray examination at this time showed a very diffuse shadow density in the right upper pulmonary area. This appeared somewhat like a tumor, although a pneumonic phthisis was not ruled out. The left pulmonary area showed a very distinct increase of density which had the appearance of a very florid stage of fibroid phthisis. No further developments were noted until May 1, 1921, when the superficial veins of the chest, face, scalp, arms and abdomen were found distended. Flatness was elicited over the entire right lung with exaggerated tactile fremitus and tubular breathing. Over the left lung decreased resonance throughout with bronchovesicular breathing and a few rales were heard. The patient died May 5.

Necropsy. (Dr. Stangl.) In the upper region of the mediastinum there is a hard tumor mass about 15 by 10 by 12 cm., which encloses the trachea, bronchi and large vessels of the neck. When the trachea and bronchi are opened there is found in the entire lining of the right bronchus numerous white nodules and ulcerating white cancerous areas. The lumen of this bronchus admits with difficulty the tip of the little finger. The left bronchus is free and its lining is unchanged. The right lung is firm and crepitation is absent everywhere. The pleural covering is markedly thickened and about 3 mm. in some areas. The cut surface shows a black moderately wet parenchyma in which no areas of consolidation or tubercle formation are seen. The right bronchus for a distance of 10 cm. distal to the bifurcation is surrounded by a layer of cancerous tissue, 3 mm. in thickness. The left lung is also partially collapsed, dark purple to black in color, and on palpation crepitation is markedly diminished, but no nodules or tubercles are felt. The cut surface is bloody and no areas of tubercle formation or consolidation are noted.

Anatomic diagnosis: Primary carcinoma of the right main bronchus; carcinoma invasion of the right lung and mediastinal lymph nodes; tumor compression of the right bronchus and superior vena cava. Bilateral metastatic carcinoma of the adrenal glands; metastatic carcinoma of the periaortic, abdominal, iliac and left femoral lymph glands. Extensive fibrous pleuritis; fibrous obliterative pericarditis.

CASE IV.—J. S., a white male, aged forty-five years, entered the hospital complaining of pain in both shoulders and cough of about two months' duration. Physical examination revealed findings of consolidation in the right lower lobe with compensatory emphysema. The spleen was palpable and the liver was enlarged, nodular and firm. There was marked clubbing of the fingers and toes. Roentgen ray examination of the chest, July 28, 1924, revealed two areas of increased density in the thorax, upper left and lower right thirds. Shadow density was more that of a consolidation than a tumor growth, such as metastases. The hemoglobin was 78 per cent; red blood count, 4,700,000; white blood count, 15,000. No blood was noted in the stools and bile pigments were present. The blood Wassermann was negative, and the sputum was repeatedly negative for tubercle bacilli. During the patient's stay in the hospital an appreciable increase in the size of the liver nodules was noted and he developed a tender swelling in the region of the left zygomatic bone and complained of very severe headaches. On August 18 the patient developed a paradoxical incontinence and the next day died.

Necropsy. The left lung shows hypostatic edema. The right lung crepitates in the upper and middle lobes. The lower lobe is solid and is invaded by gray-white carcinomatous tissue, and there is marked thickening of the bronchi, in one place as much as 5 cm. The carcinoma grossly appears to take its origin from the bronchi of the right lobe and extends peripherally to involve the lung tissue.

Anatomic diagnosis: Primary bronchogenic carcinoma of the lower lobe of the right lung; metastatic carcinoma of the mediastinal lymph glands, liver, kidney, left fourth rib and thoracic vertebra, left zygomatic process, the calvarium and brain and a single perigastric lymph gland; marked pulmonary osteoarthropathy.

CASE V.—W. P., a white male, aged sixty-five years, entered the hospital complaining of pain in the upper right quadrant of the abdomen, weakness, loss of weight amounting to 50 pounds in the past three months and loss of appetite. Physical examination revealed lagging and lessened breathing movements in the upper left lobe with definite dulness in the left supra-

clavicular and infraclavicular spaces. Bronchial breathing was present over the area of dullness with a few rales. The liver was one hand's breadth below the costal margin, hard, nodular and somewhat painful. The axillary glands were enlarged and nodular. The hemoglobin was 92 per cent; red blood count, 5,408,000; white blood count, 10,700. The urine contained a trace of albumin with a few hyaline and granular casts. Roentgen ray of the lungs, October 31, 1922, showed the left apex clouded; upper right lobe showed dense clouding; trachea not displaced; mottling was not proportionate for the extent of the shadow, suggesting that it may not be tuberculous. The blood Wassermann test was negative.

Necropsy. (Dr. Moody.) The right lung is mottled gray-black. No areas of consolidation. Cut surface is gray and moist. The left lung is small and compressed and in the upper lobe there is a tumor nodule 7 cm. in diameter. There are nodules of tumor tissue in the upper portion.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left lung; metastatic carcinoma of the periaortic tissues, liver, left lung, heart and pericardium; compression atelectasis of the left lung; bilateral fibrous pleuritis.

CASE VI.—A. Y., a white male, aged fifty-two years, entered the hospital, February 9, 1924, complaining of cough, bloody expectoration, loss of weight and marked weakness, with pain in the chest of four months' duration. Physical examination revealed flatness over the left lower lobe posteriorly with diminished tactile fremitus over this area and distant breath sounds. Coarse and moist rales were heard over both lungs. There was a spastic paralysis of the left arm and leg with a bilateral ankle clonus and Babinski with increased knee jerks. No rigidity of the neck; no ocular or facial paralysis. The hemoglobin was 45 per cent; red blood count, 3,500,000; white blood count, 12,600.

Necropsy. (Dr. Singer). The left lung is crepitant over the upper lobe and boggy posteriorly. The lower lobe is fluctuant over the lower three-fourths and is airless. Section of this lobe reveals the central portion to be occupied by a soft broken-down mass of tissue, enclosed in a definite capsule. The mass measures 6 by 10 cm. Most of the tissue here is soft and friable, the remainder bloody. Attached to the wall of the vein to the left lower lobe there is a white tumor mass which occludes it. Lung weighs 1200 gm. The right lung crepitates throughout and weighs 640 gm.

Anatomic diagnosis. Primary bronchogenic carcinoma of the left lung; metastatic tumor invasion of the periaortic, tracheobronchial and left bronchial lymph glands; large solitary metastatic tumor nodule of the left adrenal gland; multiple secondary tumor nodules of the brains; left serosanguineofibrinous pleuritis; parietal tumor thrombus of the first portion of the left pulmonary vein; peripheral pneumonia of the left lower pulmonary lobe; acute parenchymatous degeneration of the liver, kidneys and myocardium; hypostatic hyperemia of the lungs.

CASE VII.—W. E., a white female, aged about sixty-nine years, entered the hospital, July 3, 1924, complaining of shortness of breath, swelling of the lower extremities, cough, precordial pain and palpitation all of about four months' duration. In the past she had had repeated attacks of rheumatism. Physical examination revealed the left border of the heart to be 2 cm. outside the nipple line, the right border 2 cm. to the right of the sternum. No murmurs were heard and the tones were regular. The lungs showed dulness over the entire left chest with dullness over the right lung posteriorly. Rales were present over the entire left chest and lower part of the right. There was slight edema of the lower extremities. On July 4

the left pleural cavity was aspirated and 1400 cc. of a hemorrhagic fluid was obtained. This had a specific gravity of 1022, with a predominance of lymphocytes. Cultures showed Staphylococcus albus. The white blood count was 8500.

Necropsy. (Dr. Singer.) The lower portion of one of the primary left bronchi shows mottled white patches, not ulcerated. The mucosa covering it is normal. The left lung is about one-third normal in size and crepitation is absent everywhere. There is one nodule near the base, about the size of a large walnut, whose cut surface reveals white tumor tissue, from which a white material may be readily scrapped. The pleura is thickened and in one place there is a soft fungating mass with a fleshy surface. The remainder of the pleura is nodular and roughened. The right lung crepitates throughout. One small nodule is felt over the lower lobe, which on cut section appears fleshy.

Anatomic diagnosis: Primary carcinoma of the left lung; diffuse tumor invasion of the left pleura; metastatic tumor nodules of both lungs; carcinomatous invasion of the tracheobronchial lymph glands; multiple nodular tumor metastases of the pericardium; left hemothorax; marked compression atelectasis of the left lung; eccentric hypertrophy of the left ventricle; generalized senile arteriosclerosis; moderate dilatation of the right heart chambers; passive hyperemia of the lungs; chronic passive congestion of the abdominal viscera.

CASE VIII.—L. W., a white male, aged sixty-five years, entered the hospital, June 20, 1924, complaining of cough, loss of weight and weakness. The cough was of two months' duration, was paroxysmal in character and productive of a yellow-gray mucus and occasionally a small amount of dark brown material, with a foul odor at times. Physical examination revealed impaired resonance posteriorly over the left lower lobe of the lung, with decreased tactile fremitus on the left side. The voice sounds were diminished over the left lobe posteriorly. No changes were noted in the breath sounds. Fine crepitant rales were heard over the left lobe posteriorly. Repeated examinations of the sputum were negative for tubercle bacilli. The hemoglobin was 80 per cent; white blood count, 12,200. Roentgen ray of the chest on June 23 showed obscurity throughout both lungs more in the lower half of the right and lower fourth of the left lung. An even density of the lower half of the right lung suggests an incompletely resolved consolidation. Fleck-like densities of the upper half of the right and upper three-fourths of the left without greater involvement of the apices renders possible tuberculous character. The blood Wassermann was negative.

Necropsy. (Dr. Singer.) The lining of the trachea is everywhere covered diffusely by small nodules about 1 mm. in diameter. In the lower part of the trachea there is a black plaque larger than the others, which is puckered. The left lung is markedly scarred and covered everywhere by thick fibrous parietal pleura, particularly about the apex. There are numerous yellow nodules in the apex and upper lobe. The lower portion of the lung posteriorly is completely consolidated. The right lung weighs 820 gm., and its surface is covered by fibrous parietal pleura. The apex is nodular superficially. Nodules are also found throughout the remainder of the surface of the lung. The lower aspect posteriorly is consolidated. Both lungs contain within their substance white tumor tissue, particularly prominent about the bronchi causing in many places constriction of the lumen. Some of these nodules have undergone softening and consist of white pultaceous matter. The larger bronchi are scarred longitudinally, nodular and their lumen is constricted. This is present on both sides.

Anatomic diagnosis: Primary submucous carcinoma of the trachea with

diffuse bronchial invasion; diffuse carcinomatosis of both pulmonary lobes; tumor infiltration of the visceral and parietal pleuræ with bilateral hemothorax; carcinomatous invasion of the mediastinal lymph glands; secondary nodular carcinomatosis of the pericardium; metastatic carcinomatous nodules of the liver and adrenal glands; hypostatic bronchopneumonia.

CASE IX.—T. S., a white male, aged forty-two years, entered the hospital, August 2, 1924, complaining of pain in the left chest, back, shoulders, elbows and left lower extremity all of three months' duration. Hoarseness and night sweats had been present for three weeks prior to entrance. Loss of weight had been 35 pounds since the onset of symptoms. Physical examination revealed bilateral hard, nonmovable glandular masses in the supraclavicular fossæ. The anterior and posterior cervical nodes were enlarged on the right side. The chest and lungs showed nothing noteworthy. Laryngoscopic examination showed a paralysis of the left vocal cord and paralysis of the left side of the palate. This was ascribed to local pressure on the left recurrent laryngeal nerve. The sputum was repeatedly negative for tubercle bacilli. The hemoglobin was 60 per cent; red blood count, 3,700,000; white blood count, 9600. Roentgen ray of the chest showed the left apex to be veiled. The right apex was obscured by a small shadow extending at the chest periphery into the region dorsal to the first intercostal space, having a convex well-defined border and being of even density. This was thought to be a neoplasm within the lung. Roentgen ray examination of the gastrointestinal tract was negative. Biopsy examination of a gland removed from the neck revealed carcinomatous invasion. The patient refused to stay in the hospital and left in poor condition. This case was diagnosed as primary carcinoma of the right apex with metastases to the supraclavicular and cervical nodes.

CASE X.—J. B., a white male, aged thirty-nine years, entered the hospital complaining of pain in both shoulders. This was constant, dull aching in character and aggravated on coughing and deep inspiration. In addition, cough, weakness, loss of weight and a sharp stabbing intermittent pain beneath the sternum and radiating backward were present. Physical examination revealed the anterior chain of cervical nodes enlarged. The glands were discrete, firm, shot-like and not tender. The chest revealed poor expansion bilaterally. Over almost the entire lung was noted diminished tactile fremitus, flatness, distant tubular breathing, bronchophony and pectoriloquy. The abdomen showed moderate tenderness and slight rigidity in the left upper quadrant. The liver was three fingers' breadth below the costal margin. The hemoglobin was 55 per cent; white blood count, 10,500. The sputum was repeatedly negative for tubercle bacilli. The blood Wassermann test was negative. The condition of the patient was too poor to allow Roentgen ray examination.

Necropsy. (Dr. Singer.) The anterior mediastinum is thickened and contains nodules of tumor tissue. The tumor tissue extends well up into the neck. Along the abdominal aorta are glands containing tumor tissue. There are a number of tumor masses beneath the right parietal pleura. In cutting into the bronchi of the left lung just at the bifurcation there is a tumor nodule obstructing the bronchus to the upper lobe. The upper portion of the left lung contains a number of abscess cavities containing brownish-red fluid. There are a number of similar abscesses in the lower lobe. The upper lobe of the left lung is uniformly consolidated and granular, and for the most part gray, while in the lower lobe are circumscribed areas of consolidation. The right lung is heavy and bloody, containing a large number of raised granular areas.

Anatomic diagnosis: Primary carcinoma of the superior left bronchus

with metastases into the left lung; metastatic carcinoma of the kidneys, adrenals, liver and pancreas; carcinomatous invasion of the superior mediastinal and left cervical tissues; tumor involvement of the cervical, mediastinal and abdominal lymph nodes; secondary carcinomatous nodule in the tip of the appendix; tumor constriction of the bronchioles of the left lung with bronchiectatic cavitation and abscess formation; encysted empyema of the left pleural cavity; multiple disseminated metastatic tumor nodules in the brain; subcutaneous metastatic nodule in the left chest; pneumonic consolidation of the left lung; hypostatic bronchopneumonia of the right lung; bilateral acute fibrinous pleuritis; cloudy swelling of the parenchymatous organs.

CASE XI.—E. D., a white male, aged fifty-seven years, entered the hospital complaining of shortness of breath and cough of six weeks' duration. Physical examination revealed poor expansion, impairment of resonance, tubular breathing, bronchophony and egophony over the left lower lobe. Rales were heard scattered through the right lung. The patient sank rapidly and died, March 11, 1924. The hemoglobin was 80 per cent; white blood count, 17,400.

Necropsy. (Dr. Singer.) Left lung: The surface of the upper lobe is covered by a thick layer of parietal pleura, thickest in the lower half, measuring fully 6 mm. in thickness. The parietal pericardium is attached to the lung. Numerous nodules are felt throughout the upper lobe. On section of the upper lobe and upper two-thirds of the lower lobe the lung is wet, mottled red and black and contains numerous tumor nodules 1 to 3 mm. in diameter. The lower third of the lower lobe is very hard and on section is mottled gray with a small amount of black and has the appearance of firm fibrous tissue or tumor. No caseation is seen, but there are numerous pockets of pus. The upper margin of the tumor is sharply demarcated from the lung by firm fibrous tissue. This is roughly triangular in shape, measuring 9 by 6 by 10 cm. The lung weighs 1000 gm.

Anatomic diagnosis: Primary diffuse alveolar carcinoma of the left pulmonary lobe; carcinomatous metastases to the left upper lobe, the right lung and mediastinal lymph glands; tumor invasion of the liver and right adrenal glands; marked left fibrous pleuritis; diffuse fibrous mediastinitis; marked fatty changes of the liver; chronic diffuse nephritis; right hydrothorax.

CASE XII.—W. R., a white male, aged thirty-eight years, entered the hospital on December 2, 1921, complaining of symptoms which led to a diagnosis of chronic rheumatoid arthritis. The patient left the hospital, but returned, January 3, 1922, complaining of pain in the back and neck and swelling of the wrists and ankles. No chest findings were noted nor were there any complaints referable to the respiratory system. On February 4 the temperature suddenly became elevated to 104.8° and respirations to 26. Examination of the chest revealed dulness, tubular breathing and coarse rales over the right upper lobe. Posteriorly at the angle of the scapula dulness tubular breathing and coarse rales were noted. The hemoglobin was 90 per cent; red blood count, 4,816,000; white blood count, 21,150. The sputum was repeatedly negative for tubercle bacilli. The Wassermann test was negative both in blood and spinal fluid.

Necropsy. (Dr. Moody.) The right lung weighs 400 gm. Under the pleura in the lower lobe there are a number of small white nodules 1 to 3 mm. in diameter, and these are scattered throughout the lower lobe but nowhere else. Crepitation is everywhere present, although there is slight loss of elasticity. On cut section there are a number of small tumor masses in the tissue of the lung. The left lung weighs 1880 gm. The

pleural surface of the upper lobe is everywhere studded with tumor masses. It is quite solid, airless and in the lining of the bronchi there are a number of white tumor masses, particularly in the left bronchus below its bifurcation. Cut surface of the upper lobe shows the lung tissue to be practically invaded everywhere by tumor tissue. The lung is solid and in the region of the larger bronchi there is more tumor than at the periphery.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left lung; metastatic carcinoma of the peribronchial and periaortic lymph glands, right lung, liver, both adrenals, pleura, pericardium and costochondral cartilage of the third and fourth ribs; clubbing of the fingers and toes; compensatory emphysema of the right lung; pathologic fracture of the costochondral junction of the third and fourth ribs; scar of the glans penis; syphilitic aortitis.

CASE XIII.—M. H., a colored female, aged seventy years, entered the hospital, January 27, 1924, complaining of shortness of breath of five weeks' duration, productive and persistent cough, orthopnea and swelling of the ankles of three weeks' duration. At the time of admission the dyspnea was so severe that the patient was unable to speak, was very restless and gasped for air. On physical examination the chest showed a filling out of the intercostal spaces on the right side. Resonance was absent, expansion limited, breath sounds suppressed and tubular, tactile fremitus was absent and voice sounds were suppressed over the entire right chest. The left lung was practically normal. The heart showed a forceful apex beat situated in the eighth interspace in the anterior axillary line. The tones were weak and rapid. No murmurs or thrills were present. The liver extended four fingers' breadth below the right costal margin. There was moderate edema of the ankles. On January 28, 1924, the right chest cavity was tapped and 350 cc. of red-brown fluid was obtained. The hemoglobin was 90 per cent; red cell count, 3,820,000; white cell count, 9880. The urine showed albumin with hyaline and granular casts. The blood Wassermann test was negative. The blood chemistry findings were within normal limits. Roentgen ray of the chest showed obscurity of the whole right lung with displacement of the heart far to the left. The left lung was negative.

Necropsy. (Dr. Singer.) The left lung appears small, moist and red, especially in its dependent portion where much frothy red fluid can be expressed. The right lung is collapsed against the vertebral column. The outer surface is covered with fibrin. In no portion is it crepitant. It is nodular irregularly throughout. On cutting into the bronchus of the upper lobe a point of constriction is met just beyond the bifurcation of the main bronchus, about which white tumor tissue is seen extending along the bronchus. No distinct ulceration is noted of any of the bronchi. Diffuse deposits of tumor tissue are seen throughout the lung measuring 2 mm. to 2 cm. in size.

Anatomic diagnosis: Primary carcinoma of the right bronchus; tumor metastases throughout the right lung; metastatic carcinoma of the tracheobronchial, bronchial, periaortic, peripancreatic and peribiliary lymph glands; secondary carcinomatous deposits in the liver; right hemothorax; compression atelectasis of the right lung; localized right bronchiectasis; acute right fibrinous pleuritis; healed tuberculosis of the tracheobronchial lymph nodes; fibrous thickening of the apical pleura of both lungs; early metastatic invasion of the left parietal pleura; brown pigmentation of the liver and myocardium; multiple acute ulcers of the duodenum.

CASE XIV.—J. S., a white male, aged fifty years, entered the hospital, March 18, 1921, complaining of pain in the neck and head, pain in the

shoulders and hips, pain in the chest, cough and expectoration. Pain in the chest first started on the left side then shifted to the right side. Physical examination revealed marked tenderness on pressure over the cervicodorsal region of the spine. The lungs showed decreased resonance over the left lower lobe with many mucus rales throughout the chest. The liver was two fingers' breadth below the costal margin. Repeated examinations of the sputum were negative for tubercle bacilli. On May 2 the left chest cavity was aspirated and a bloody fluid was obtained which showed 72 per cent polymorphonuclears and 27 per cent lymphocytes. The blood Wassermann test was negative. The red blood count was 4,064,000; the white blood count, 12,500. Roentgen ray of the chest, April 14, showed moderate amount of diffuse fibrosis in the right lung. The left lung showed similar fibrosis in the upper portion, while the lower lung area was obliterated by greatly increased shadows due partly to a greatly thickened costal pleura. On April 23 Roentgen ray revealed the entire left side occupied by a shadow density characteristic of fluid.

No change was noted in the patient's condition until April 10, when he developed a left-sided anesthesia with also right sided involvement. Neurologic diagnosis was Brown-Sequard paralysis, due either to a vertebral lesion or extradural spinal tumor. Roentgen ray of the cervical spine was negative. On April 26 several small hard nodules were felt in the abdominal wall; one was removed and examined microscopically and showed infiltrating actively dividing cells typical of malignancy.

Necropsy. (Dr. Wells.) May 17, 1921.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left lung with suppurative bronchitis, atelectasis and abscess formation in the left lower lobe; tumor metastases in both adrenals, both kidneys, both iliac bones, right seventh rib with pathologic fracture, left twelfth rib with pathologic fracture, neck of the femur with pathologic fracture and right pleura; solitary metastases in the right lung; subcutaneous metastases in the abdominal wall and both axillæ; two tumor metastases in the left cerebral hemisphere; metastases in the occipital and base of sphenoid bone with compression of the medulla, in the pancreas and in the hilum of left kidney, in the mesentery, in epicardium and in the mesogastric lymph nodes; healed tuberculous scars in both lungs, healed caseous tuberculosis of the right peribronchial lymph nodes.

CASE XV.—M. W., a white male, aged fifty-seven years, entered the hospital complaining of a nonproductive cough, pain in the right side of the chest and paroxysmal dyspnea. The duration of these symptoms was five weeks. Painless swelling of the right side of the neck and of the left arm were noted three weeks prior to entrance. Physical examination revealed a marked prominence of the left side of the neck, due to cervical adenopathy, consisting of painless, discrete, hazel-nut-sized glands. The axillary nodes were enlarged more markedly on the right side. The left forearm was edematous. The chest revealed limited expansion especially on the right side. Vocal fremitus was increased on the right side and percussion showed flatness over the entire right lung. Breath sounds were heard with diminished intensity over the right lung. Over the left lung posteriorly from the second to the sixth dorsal spine bronchial breathing, bronchophony and slight egophony were heard. The hemoglobin was 80 per cent; red cell count, 3,150,000; white cell count, 12,000. Roentgen ray of the chest, January 16, 1924, revealed a defective right diaphragm, indefinite cardiac and arch borders, much fibrosis of the right lung with infiltration diminishing toward the periphery on the right. An irregular cavity was noted near the right hilum and deviation of the trachea. Biopsy of a cervical gland showed secondary carcinoma. The patient died Janu-

ary 28; no necropsy was obtained. This case was diagnosed as primary carcinoma of the right lung with metastases to the cervical glands.

CASE XVI.—S. A., a white male, aged sixty years, entered the hospital, September 10, 1922. No history of his complaints could be obtained, because of his inability to speak English. Physical examination revealed slight cervical adenopathy. The right side of the chest appeared larger than the left. Vocal fremitus was slightly increased low down over the left base. Percussion revealed a flat note over the lower lobe. Breath sounds were harsh everywhere except over the left base, where they were heard poorly. Coarse moist rales were present over all parts of the lungs. During the course of the examination the patient expectorated a bloody fluid, dull pinkish in color and foul smelling. No tubercle bacilli were found in several specimens of sputum. Expectoration of large quantities of sputum continued. The hemoglobin was 60 per cent; red cell count, 3,500,000; white cell count, 40,000.

Necropsy. (Dr. Singer.) The right lung weighs 820 gm.; its surface is smooth; crepitates throughout, less in the lower portions. A few solid areas are noted throughout. The lower lobe is dark red and bloody. There are numerous small red raised granular areas solid in consistency. The left lung is covered by numerous fibrous tags. Posteriorly the parietal pleura is adherent. The lower lobe is increased in consistency, and there is definite evidence of cavitation. On section the upper lobe is solid, red and fleshy. The lower lobe is replaced by a cavity filled with dirty gray fluid with thrombosed vessels coursing through it. The walls are firm and appear fibrous. There is a large patent bronchus leading to this cavity.

Anatomic diagnosis: Primary ulcerating carcinoma of the left bronchus with metastases to the left lung and to the tracheobronchial lymph nodes; huge abscess cavity of the left lower pulmonary lobe; compression atelectasis of the left upper lobe; bronchopneumonic foci of the right upper lobe; marked hypostatic hyperemia and edema of the right lower lobe; marked senile sclerosis of the aorta with atheromatous ulceration and calcification; partial obliterative left fibrous pleuritis.

CASE XVII.—J. B., a colored male, aged fifty years, entered the hospital, December 26, 1920, complaining of weakness, dyspnea and coughing of blood of four months' duration. Physical examination was essentially negative except for the findings of a pleural effusion over the entire right chest. Paracentesis thoracicis revealed a straw-colored fluid; specific gravity, 1013; 75 per cent polymorphonuclears and 25 per cent lymphocytes and no bacteria. The Wassermann tests of both the blood and spinal fluid were negative. Roentgen ray showed extensive pleural exudate on the right side with the entire left thorax of normal appearance.

Necropsy. (Dr. Wells.) The right lung does not collapse and is very heavy, weighing 2400 gm. with the trachea. The lower lobe is completely and uniformly consolidated, except at its inferior margin; the upper lobe is also consolidated except the anterior fourth. The densest consolidation in all of these is nearest the hilum. This consolidation is uniform except on the surface, where it is nodular. Opening into the right main bronchus finds it completely plugged to within 15 mm. of the bifurcation by a mass of necrotic tissue. The mucous membrane about this is reddened. Cut section shows a diffuse grayish consolidation, with areas of suppuration in the peripheral portion. There are white tumor nodules in the middle lobe. In the upper lobe there is a mass of white tissue involving the hilum of the lung and continuous with the necrotic mass in the main bronchus.

Anatomic diagnosis: Primary bronchogenic carcinoma of the right main

bronchus with metastases in the left lung; metastases in the mediastinal and cervical lymph glands, left kidney and sixth left rib with pathologic fracture; subcutaneous metastases over the third left costal cartilage and left parietal pleura invading the pericardium; unresolved suppurative bronchopneumonia of the right lower and middle lobes; right serofibrinous pleuritis; left hydrothroax; acute and chronic vegetative mitral endocarditis.

CASE XVIII.—A. P., a white male, aged thirty-three years, entered the hospital, February 7, 1923, complaining of dyspnea, cough and expectoration of foul-smelling brownish sputum. In addition, loss of weight and strength was also complained of. The physical examination revealed the right eyelid to be markedly swollen and the left eyelid less so. The nose was also involved in the swelling. The neck was swollen and puffy and there was a similar swelling over the sternum. The respirations were labored. Over the left chest the percussion note was hyperresonant, the breath sounds were increased and tactile fremitus was increased. Over the right chest dulness was elicited inferiorly with hyperresonance at the clavicle, cavernous breathing was heard just below the clavicle. The heart was negative.

Necropsy. (Dr. Singer.) The left lung weighs 1500 gm., is greatly enlarged and boggy. The cut surface is wet and at the posterior portion of both lobes there are a number of raised granular areas. The right lung is tightly adherent to a large irregular mediastinal mass. The pleura over it is thickened to 3 mm. On cut section of the lung there is a large amount of tumor tissue in the lower portions of the upper lobe, measuring 9 by 6 cm. The remainder of the upper lobe is firmly consolidated and from its surface and from cavities communicating with its bronchi a foul smelling purulent fluid can be expressed. The lower lobe is partially consolidated, especially in the posterior portions. In the anterior portion there are a number of cavities which almost entirely replace the parenchyma with necrotic lining, three of which measure 4 cm. in diameter. Attached to the lung in the anterior mediastinum is a firm nodular mass of tumor tissue, through which the superior vena cava courses and a large sound is passed through with only slight difficulty. This tumor mass measures 11 by 10 cm.

Anatomic diagnosis: Primary bronchogenic (?) carcinoma of the right upper lobe with metastases in the mediastinal glands and tissue with partial obstruction of the superior vena cava; bronchiectasis and bronchiectatic cavitation of the entire right lung; pneumonic consolidation of remainder of right upper lobe and anterior portion of lower; right fibrous obliterative pleuritis; edema of tissues of head and neck, upper thorax and upper extremities; varices of superficial veins of both shoulder regions.

CASE XIX.—F. S., a white male, aged forty-four years, entered the hospital, November 9, 1919, complaining of cough, hemoptysis, dyspnea, weakness, pain in the chest and loss of weight. These symptoms were about of two months' duration. Physical examination showed partial consolidation of both upper lobes posteriorly and the right upper anteriorly. Rales were heard over the remaining portions of the lungs. The liver was 6 cm. below the costal margin and the extremities showed slight osteoarthropathy. The sputum was repeatedly negative for tubercle bacilli. Roentgen ray of the chest showed a dense mass shadow in the left hilum extending in all directions into the lung area. While not definitely circumscribed, this had the appearance of a tumor of the hilum.

Necropsy. (Dr. Wells.) The upper lobe of the left lung is infiltrated with tumor tissue in about two-thirds of its extent reaching in places to the pleura. At the lower margin of the left upper lobe there is a pus-filled

cavity lined with a pyogenic membrane. There is another area of softening nearly black in color and another of beginning suppuration. The tumor extends along the large bronchi and vessels about 5 cm.; from there to the periphery the upper lobe is largely consolidated. The lower lobe is boggy and full of fluid with only a few small areas of bronchopneumonia. The extension of the tumor within the lung is in the form of dense white tissue growing from the hilum into the upper but not the lower lobe. The tumor has invaded the main left bronchus at the origin of the superior division. The bronchus here is nearly occluded and the mucosa ulcerated. The right lung is free from tumor tissue and shows only an area of hypostatic bronchopneumonia.

Anatomic diagnosis: Primary bronchogenic carcinoma of the left upper lobe of the lung; metastases in the liver, thyroid, bones, spleen, adrenals, right kidney, left tonsil, tongue, trachea, ileum, appendix, pancreas, neck of the gallbladder; extensive infiltration of the cervical, mediastinal and retroperitoneal lymph glands; gangrene and abscess formation in the left upper lobe; hypostatic edema and bronchopneumonia of both lungs; fatty infiltration of the liver.

CASE XX.—C. S., a white male, aged thirty-one years, entered the hospital, March 15, 1917, complaining of severe frontal headache, failing of vision in the right eye, cough, loss of weight and night sweats. Headaches had been present for the past two years, while the other symptoms had been only of six months' duration. Physical examination showed that the pupils reacted sluggishly to both light and accommodation. There was limited expansion over the left side of the chest. Over the right lower lobe flatness with absent breath sounds was noted. The heart was displaced to the right, but otherwise was normal. Findings were present of a left-sided hydrothorax. Repeated puncture of the chest showed a serous hemorrhagic fluid much less than was expected. The blood Wassermann was negative.

Roentgen ray examination of the chest revealed a very dense shadow in the left lower lobe, the outline of which was smooth and rounded. It was centrally located, the outer portion of the lung area being very clear. This was thought to be a tumor. Subsequent examinations corroborated this finding.

Necropsy. (Dr. Nuzum.) The left pleural cavity is completely obliterated by fibrous adhesions. There is a walled-off cavity containing pus. The left lung weighs 1800 gm. The pleura covering it is dull, opaque and thickened throughout. The lung is uniformly solid, no single nodular areas being palpable. On cut section it is difficult to ascertain where the tumor growth arises, although it appears to extend from the larger bronchi. The left lower lobe is extremely firm, except for various areas which have undergone softening. These contain purulent material. The right lung shows numerous areas of bronchopneumonia with marginal emphysema.

Anatomic diagnosis: Primary bronchogenic carcinoma of the lower lobe of the left lung; left-sided obliterative fibrous pleuritis; metastatic carcinomatosis of the peribronchial and periaortic lymph nodes; disseminated pseudolobar bronchopneumonia; mucopurulent tracheobronchitis; marginal emphysema of the right lung; passive hyperemia of the liver and spleen; cloudy swelling of the myocardium; fatty changes of the liver and kidney.

CASE XXI.—A. W., a white male, aged thirty-six years, entered the hospital, July 22, 1918, complaining of cough, dyspnea, loss of appetite and loss of weight. His illness was of but six weeks' duration. Physical examination revealed flatness over the left lung with some suppression of the breath sounds. Sibilant and moist rales were heard over the right

lung. On August 18 the left chest cavity was tapped and much pus was obtained. The white cell count was 30,000. The sputum was repeatedly negative for tubercle bacilli. Roentgen ray examination of the chest showed obliteration of the lung shadows of the left chest as high as the clavicle. The heart shadow could not be distinguished. The esophagus was crowded slightly to the right and forward and was pressed upon sufficiently to cause temporary obstruction and dilatation three fingers' below below the sternal notch.

Necropsy. (Dr. D. J. Davis.) The right lung is normal except for fibrous tags on its surface. The left lung surface is studded with numerous white nodules, varying from the size of a pinhead to 5 cm. in diameter. White masses extend through the mediastinum. Cut surface reveals numerous similar nodules, more numerous about the hilum and lower portions of the lung. Retention abscesses are seen which exude green slimy pus. The bronchial tubes are greatly thickened and exude pus. A large mass is situated just below the bifurcation of the trachea which presses upon and involves the left main bronchus.

Anatomic diagnosis: Primary carcinoma of the left bronchus; secondary carcinoma of the lungs, pleura, mediastinal tissues and pericardium; metastatic carcinomatous nodules in the capsule of the liver; retention abscess in the parenchyma of the left lung; bilateral fibrinous pleuritis; massive anemic infarcts of the spleen and both kidneys; thrombosis of the branches of the hepatic artery; left-sided seminovesiculitis; rupture of a metastatic carcinomatous nodule into the general peritoneal cavity.

CASE XXII.—F. J. D., a white male, aged forty-five years, entered the hospital, June 1, 1921, complaining of cough, loss of weight, weakness and loss of appetite. His illness was of eight months' duration. Physical examination revealed impaired resonance over the left lower chest posteriorly below the level of the seventh dorsal vertebra, extending outward to the midaxillary line. Breath sounds diminished over this area of dulness. Crackling rales were heard over the left apex. There were no findings over the right lung. Roentgen ray examination revealed a shadow in the left lower thorax, indicating pleural pathology. The blood Wassermann test was negative.

Necropsy. (Dr. Wells.) The left lung is completely collapsed. Its pleura is everywhere thickened to about 1 to 3 mm. On palpation the lung has a water-logged, rubbery feel. On cut section of the upper lobe a diffuse mass of cancerous tissue, 6 cm. in diameter, surrounds the left bronchus and bronchioles. The lining of the bronchus is roughened and cancerous ulcerative tissue can be seen in the lining. The lower lobe on section is found filled with dark green, very foul smelling pus. The right lung is normal except for congestion.

Anatomic diagnosis: Primary bronchogenic ulceromedullary carcinoma (left), with metastases to the tracheobronchial, periesophageal, perigastric, peripancreatic lymph glands; metastatic carcinoma of the liver and dura mater; left-sided empyema with complete atelectasis of the left lung; abscess of the lower lobe of the left lung; marked left-sided fibrous pleuritis; hypostatic hyperemia and edema of the right lung; marked dilatation of the stomach due to hemorrhage into it; pachymeningitis externa.

CASE XXIII.—S. W., a white male, aged fifty-five years, entered the hospital, August 3, 1924, complaining of pain in the left hip of four months' duration, and in addition loss of weight. Physical examination revealed an enlarged submaxillary and posterior cervical node on the left side. The glands were firm, discrete and movable. The lungs showed flatness over the entire left chest anteriorly and posteriorly as high as the third

dorsal spine with impaired resonance above this. Bronchial breathing was present over the left apex posteriorly, while the breath sounds were absent over the lower anterior and posterior chest on the left side. Tactile and vocal fremitus was absent over this region. There were a few moist rales over the right base posteriorly. There was bilateral inguinal adenopathy, and marked tenderness was present over the left iliac crest. Pain was elicited on moving the left leg and swelling was noted below the left iliac crest and over the great trochanter. The blood Wassermann was negative and the sputum was repeatedly negative for tubercle bacilli. Aspiration of the left chest cavity revealed a yellow-brown serous fluid, which contained a great number of lymphocytes and erythrocytes. The white blood count was 14,000; red cell count, 3,800,000; hemoglobin, 80 per cent. Roentgen ray examination of the chest showed the heart displaced to the left slightly, indicating much fibrosis, despite the fact that a fluid level of hydro-or pyopneumothorax was seen at the height of the first intercostal space, which with pleural thickening obliterated the rib shadows.

Necropsy. (Dr. Rappaport.) The left lung weighs 1200 gm. with attached pleura. Its surface is covered with thick fibrous pleura. Crepitation is absent, the lung being nearly solid. Cut surface reveals mottled yellow-white and black surfaces and consolidation, except for the apex and portions of the inferior lobe. The right lung crepitates throughout and its cut surface appears grossly unchanged.

Anatomic diagnosis: Primary diffuse carcinoma of the left upper lobe; nodular carcinomatous metastases to the left pleura; left serofibrinous pleuritis with compression atelectasis of the left lower pulmonary lobe; carcinomatous metastases to the iliac crests; metastatic carcinoma to the tracheobronchial, cervical and axillary nodes; miliary disseminated carcinomatous nodules of the epicardium and peritoneum; nodular carcinomatous metastases to the liver and kidneys; solitary ulcerating carcinomatous nodule of the ileum; right focal fibrous pleuritis.

CASE XXIV.—J. C., a white male, aged fifty-five years, entered the hospital, February 11, 1920, complaining of pain in the right arm and scapular region for the past eight weeks; cough productive of blood-tinged sputum of one week's duration and night sweats for one week. Loss of weight, loss of appetite and weakness were also complained of. Physical examination revealed the cervical chain of glands on the right side definitely enlarged. The left lower lobe of the lung was dull, and breath sounds were diminished. Posteriorly over the right upper lobe resonance was diminished and breath sounds were exaggerated. The heart was enlarged in all diameters and the tones were faint, but regular. There was spasm and tenderness of the right trapezius, with atrophy and weakness of the right hand. This indicated pressure on the brachial plexus by the enlarged cervical nodes. The white blood count was 18,000, and the sputum was repeatedly negative for tubercle bacilli. Roentgen ray examination revealed a disappearance of the transverse process of the seventh cervical vertebra on the right side, suggesting a metastatic malignancy at this point. The thorax contained a marked shadow density situated in the left hilum area extending outward into the lung. Biopsy examination of a cervical gland showed a mass of infiltrating carcinoma cells. The patient was given a few Roentgen ray treatments for carcinoma of the lung. His complaints continued without improvement and against advice he signed a release and left the hospital.

This case was diagnosed as primary carcinoma of the lung (left) with metastases to the cervical nodes and seventh cervical vertebra.

Summary and Conclusions. Primary carcinoma of the lung is not as rare a clinical condition as has been described in the past, and the condition can be diagnosed antemortem.

The striking increase in the number of tumors of the lung since the influenza epidemic suggests some relation between these two conditions.

Pulmonary cancer presents a very varied pathologic picture, not only as to gross and microscopic characteristics, but also as regards the associated pathology.

Metastases occur early and are very widespread.

Histogenesis presents many difficulties, because of the morphological variations in the cells concerned and the difficulty in obtaining the tumors in the early stages for study.

Efforts to classify these tumors as to histogenesis admit great probability of error. However, from authentic studies it appears that origin from bronchial mucosa is most frequent and that origin from alveolar epithelium is very rare.

There are no pathognomonic symptoms of tumor of the lung; weakness, cough, expectoration, pain in the chest and dyspnea being most important.

With more frequent use of the bronchoscope and with an appreciation that primary carcinoma of the lung is not rare, this clinical entity will be diagnosed more commonly antemortem.

The use of the bronchoscope both for diagnosis and treatment opens a field in a condition where formerly the prognosis was very poor.

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REVIEWS.

THE NORMAL DIET. By W. D. SANSUM, M.S., M.D., Director of the Potter Metabolic Clinic, Department of Metabolism, Santa Barbara Cottage Hospital, Santa Barbara, Calif. Pp. 72; 1 illustration. St. Louis: C. V. Mosby Company, 1925.

IN this work the author attempts a brief exposition of "the fundamental principles of diet for the mutual use of physicians and patients." In a work as brief as this the author might better have omitted Chapter IV, entitled "Acidosis," containing, as it does, little of proven value and much which is, to say the least, controversial. It has never been proved, for example, that an acid dietary is a factor in producing migraine or bloodvessel and kidney disease. Again the emphasis which the author places on the neutralization of foods producing an acid ash by alkaline ash foods seems hardly justifiable in the light of what is known of the "buffer" action of the blood. In the remaining chapters the requirements of the body with respect to protein, bulk, water, minerals, vitamins and total calories are dealt with in a far more satisfactory manner. J. A.

TREATMENT OF KIDNEY DISEASES AND HIGH BLOOD PRESSURE. Part I. Practical Manual for Physicians and Patients. By FREDERICK M. ALLEN, M.D., Director of Physiatric Institute, Morristown, N. J. Pp. 206. Newark, N. J.: Newark Printing Company, 1925.

THIS book is an exposition of the author's own views on the treatment of kidney disease and its manifestations. He considers the subject under three headings—nitrogen retention, edema and high blood pressure. He advocates for the first a low protein diet and for the last two a salt-free diet. His discussion of nitrogen retention and of edema is in the main consistent with the views of other students of kidney disease. His views as to the causation and treatment of high blood pressure have not yet received general confirmation from other workers in the field. His directions for giving low protein and salt-free diets are the most useful features of the work. The book contains, however, many dogmatic state-

ments, the accuracy of which cannot be accepted as established, and this detracts seriously from its value and is especially objectionable if the book is to be placed, as its title suggests, in the hands of patients who are without any basis for discriminating between hypothesis and established fact. J. A.

I. The Electrochemical Factor in Neurology. By Ernest H. Pasqué. II. New Concepts of Physics. By Calvin Samuel Page. Pp. 604; 23 illustrations. Detroit: Atomic Research Association, 1925.

The nature of this volume will be apparent, without further comment by the reviewer, from the following typical quotation (p. 476): "Rx is heat; currents of Rx are electricity; Rx is the sustaining force of the atmosphere; the lungs are the dynamo of the body and, collecting Rx from the air, they create the electrical currents that supply the heat and nervous force of animal life." M. J.

A Textbook of Pathology: General and Special. For the Use of Students and Practitioners. By J. Martin Beattie, M.D., Professor of Bacteriology, University of Liverpool, etc., and W. E. Carnegie Dickson, M.D., Pathologist to the West End Hospital for Nervous Diseases, London, etc. Third edition. Pp. 1103; 499 illustrations and 17 colored plates. St. Louis: C. V. Mosby Company, 1925. Price, $11.00.

The thirteen chapters of the first part of this book are on general pathology, and occupy slightly less than one-half the volume. They treat the conventional topics of retrogressive changes, atrophy inflammation, tumors, parasites and so forth in a sound conventional manner. In the same way the twelve chapters of the second part on special pathology discuss the diseases of the various tracts in the customary anatomic sequence of systematic textbooks of pathology. Nor is this treatment without advantage to students, fresh from their anatomic studies, as long as they realize that the subject of pathology may have other methods of approach and that the field of morbid anatomy thus covered is far from comprising the whole subject of pathology. The one hundred and five pages on parasites reflect the progressive and accurate activity of the British in this field. The bone marrow, too, as one would expect from the junior author, receives more adequate attention than is customary in pathologic textbooks, especially in the beautiful colored plates.

But few errors, scriptural and typographical, have been observed. On p. 513 the streptococcus of subacute bacterial endocarditis is designated "hemolytic" instead of "viridans." The reference to Plate XIV on p. 652 should be Plate XIII. Some of the colloquial English terms, for example, "hard-bake spleen" for multiple focal caseous tuberculosis of that organ will be useless for American readers; neither would the reviewer retain "primary splenomegaly" as a synonym for splenic anemia; but these are unimportant details. For this edition the two original volumes, General and Special, "have now been published both separately and also incorporated into a single volume." The reviewer's copy, which falls into the latter category, seems of perfectly usable size. E. K.

THE PHYSIOLOGY OF MIND. By FRANCIS X. DERCUM, A.M., M.D., PH.D., Professor of Nervous and Mental Diseases, Jefferson Medical College, Philadelphia. Second edition. Philadelphia and London: W. B. Saunders Company, 1925. Price, $3.50.

AN interestingly written book, the "object and scope" of which "is to present the basic facts of those reactions of the organism to the environment" which constitutes "mind."

Beginning with most primitive responses of protoplasm, more elaborate mechanisms of receiving and transmitting "impacts" are traced through their development to the complex nervous systems of higher mammals. Psychology of man is presented together with a final appendix on Freudism, which is termed "puerile."

Perhaps some principles of transmission of impacts by means of synaptic contacts should be stated more conjecturally, but the whole is a scholarly presentation which commands deep respect and enriches the intellect of the reader. E. B.

TEXTBOOK OF DIFFERENTIAL DIAGNOSIS OF INTERNAL MEDICINE. By M. MATTHES, M.D., Professor of Medicine and Director of the Medical Clinic, University of Königsberg. Authorized translation of the fourth German edition, with extensive additions by I. W. HELD, M.D., and M. H. GROSS, M.D., New York City. Pp. 908; 176 illustrations, some in color. Philadelphia: P. Blakiston's Son & Co., 1925.

THIS work should be particularly valuable for the practitioner, as well as the internist and student. It presents the subject in a clear, logical, adequate manner; the positive characteristics of a

disease are first described and then the various conditions with which it might be confused are enumerated and the differentiating points explained. The translators have made many valuable additions to the work, bringing it up to date, as well as expressing current American views. The translation, for the most part well done, is open to some minor criticisms. There has been undue adherence at times to the original in the matter of German idiom, with, as a result, unidiomatic English. There are used many Latin terms, so common in German medical writings, but which seem stilted and out of place in English when substituted for well-known English words, as "typhus abdominalis," "lepra," "tertiano," "quartano," "colica mucosa," "porta" of entrance, and the like.

R. K.

SELECTED PAPERS: SURGICAL AND PATHOLOGICAL. By F. T. PAUL, D.Sc., (LIVERP., HON. CAUS.), Ch.M. (LIVERP.), F.R.C.S. (ENG.), Consulting Surgeon, Liverpool Royal Infirmary. Pp. 284; 23 illustrations. London: Baillière, Tindall and Cox, 1925.

TWENTY-TWO miscellaneous contributions to surgery and pathology collected by the author's colleagues on the occasion of his seventy-fifth birthday.

E. K.

THE ART OF MEDICAL TREATMENT. By FRANCIS W. PALFREY, M.D., Visiting Physicians, Boston City Hospital; Instructor in Medicine, Harvard University. Pp. 463. Philadelphia and London: W. B. Saunders Company, 1925.

THE advent of a medical mentor willing to point the nuggets from that greatest of treasures, his own experience, is an event which the student, intern and young physician will hail with keen pleasure.

Prognosis and "what to tell the family" is the bugbear of the inexperienced. Realizing this, the author has undertaken to point out in each disease what information should be imparted to the patient and what to the responsible relative or friend. The author truly propounds the art of treatment of patient and anxious relation. In every paragraph devoted to this subject the reader may find a concise, thoughtful and well-weighed statement of the prognosis to be expected in the light of modern treatment.

In the matter of treatment there is no radical departure from that which is accepted as standard by modern textbook writers. Some of the gastrointestinal therapy excludes modern methods one might expect to see there, on the basis that the older ones have proved

just as effective in the author's hands. The thoughts on stimulation, diet quackery and cults are far too fine to be relegated to the unused limbo of "appendices," and should, we feel, precede the portions dealing with treatment of systemic diseases.

The book represents a splendid balance between common sense and modern medical practice. It should be voluntarily on the young practitioner's desk and by compulsion on that of the senior medical student. C. L.

WILLIAM CADOGAN (HIS ESSAY ON GOUT). By JOHN RUHRÄH, M.D., Professor of Diseases of Children, University of Maryland. Pp. 114; 1 illustration. New York: Paul B. Hoeber, 1925. Price, $1.50.

REPRINTED with corrections from the *Annals of Medical History* of last March. The text of Cadogan's *Essay* is preceded by some biographic notes and succeeded by Mrs. Ireland's poetical review, "The Doctor Dissected, or Willy Cadogan in the Kitchen." One regrets the initial split infinitive. E. K.

ARTIFICIAL SUNLIGHT AND ITS THERAPEUTIC USES. By FRANCIS H. HUMPHRIS. Second edition. Pp. 203. Oxford Medical Publications, 1925.

THIS book is on the whole a very good survey of the general field of ultraviolet therapy for the practitioner. The technical descriptions, making allowance for the fact that the apparatus described is of British rather than American manufacture, are sufficiently detailed to be usable and contain many excellent points with reference to the standardization of equipment, measurement of degrees of reaction, etc. The therapeutic sections of the book reflect perhaps a little too much the optimism which actuates workers in a new field. It is to be regretted that no more satisfactory quantitative measurement of short wave-length dosage than that provided by distance and time is available. The author notes, but has no observations to assist in estimating, the decline in output of quartz lamps under continued use. The range of therapeutic applicability, according to the author, is practically immeasurable, and brief paragraphs are given to everything from ptyriasis (*sic*) to old age. But it is an injustice to speak too ironically of the enthusiasm of a worker in a virgin field, especially when he has written a serviceable little book containing many valuable experimental and technical points for workers with this extremely important therapeutic agent. J. S.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Factors in Causation of Gall Stones.—According to MOYNIHAN (*Brit. Méd. J.*, 1925, 1, 393), the two factors necessary for the causation of gall stones are infection and an increased amount of cholesterol in the blood. Infection may be in the accessory sinuses, the teeth, any part of the digestive or urinary tracts or in extraabdominal foci. If the infection is brought by the bile the mucosa is first attacked; if by the blood, the submucosa; if by the lymphatics, the serous coat. The author believes that infection of the gall-bladder wall always precedes gall-stone formation. In 100 consecutive cases cultures showed Bacillus coli to be present 48 times; streptococci, 8; double infection, 5; Bacillus pyocyaneus, 2; other organisms, 33. The infection causes a mucous catarrh, with stagnation deposition of the relatively translucent cholesterol and gradually of calcium. The solitary stones of pure cholesterol are not considered to be due to infection. In the examination of the gastric contents of 77 cases, achlorhydria was found in 17; hypochlorhydria in 3, a low normal acidity in 14, normal in 18, high normal in 8 and hyperacidity in 17. Chauffard's low-cholesterol diet is used, that is, skimmed milk, milk and vegetable soup, rice, macaroni, tapioca and so forth, white and lean meat, nonoily fish (boiled or baked), cereals, potatoes (not fried), green vegetables and mild cheeses.

End Results in Splenic Anemia With and Without Splenectomy.—HANRAHAN (*Arch. Surg.*, 1925, **10**, 639) has studied 35 cases of splenic anemia (22 of which had had splenectomy performed) from the points of view of etiologic factors, characteristic blood pictures, duration of symptoms, prognosis and early and late effects of splenectomy. Cases with suggested causes, such as syphilis (4), malaria (7), tuberculosis and other infections, were included, as it was felt by the author that pictures indistinguishable from the splenic anemia of unknown etiology

were produced. The unsatisfactory results of studying the morbid anatomy of splenomegalies is emphasized, the changes in all fibrotic spleens being very similar. Dividing the patients into two groups, (1) those acutely ill with symptoms referable to the anemia and (2) those presenting the picture of a chronic process, the author found that the first group might last from six to eighteen months, with fatal outcome, uninfluenced by splenectomy. In the second group splenectomy is of value, though this type of disorder is not invariably fatal without the operation, and it does not always cure the condition. In the non-operative cases the higher the color index, and the more marked the leukopenia, the worse the prognosis. In the splenectomized cases the color index seems to be immaterial, but not the leukopenia.

Systemic Liver-spleen Disease.—HANAU (*Monatsschr. f. Kinderh.*, 1924, 29, 54) considers that a liver-spleen syndrome of constitutional origin may follow cirrhosis of the liver in children, due in turn to some congenital anomaly. He describes 4 such cases (3 of which came to autopsy), and discusses 30 culled from the literature. Their ages were two and twenty-one months, eleven and fourteen years. In 3 the abdomen had been known to be large since birth, with big liver and spleen, and jaundice during the first three months of life. In the oldest patient the trouble began at the age of twelve years, after influenza; temporary improvement followed irradiation of the spleen, but soon the picture of Banti's disease supervened together with speech disturbances and paralyses. Autopsy failed to reveal the nature of the disorder.

SURGERY

UNDER THE CHARGE OF

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Intravenous Use of Metallic Mercury (Mercodel) in the Treatment of Syphilis.—ROTHWELL and MALONEY (*Am. J. Syph.*, 1925, 9, 413) state that intravenous injection of metallic mercury suspensions produce prompt clinical response in syphilis. There is no serious danger in their use, no apparent harm to the vital organs being noted. If used in small doses, 5 cc., the only reaction, if any, is a mild stomatitis. In larger doses, however, a severe stomatitis is produced in some cases. Properly administered, no phlebitis or vein thrombosis results. Primary, secondary, tertiary and cerebrospinal luetic signs have resolved under their use even when used alone. A persistently positive Wassermann has been changed even to a negative or reduced in strength of reaction. A positive spinal fluid has been changed to a negative with reduction of 37 cells to 6 cells. They do not impair the liver or kidneys.

Larger quantities of mercury may be safely administered in a shorter time than in the use of the soluble salts of mercury. No evidence of cumulative effect was elicited in twenty-two months' study of their use in a series comprising 805 injections.

Ununited Fractures.—GROVES (*Lancet*, 1925, **209**, 735) says that the causes of nonunion may be grouped as mechanical, vascular (including sepsis, sclerosis of bony canals and atrophy) and disease including infection, pyogenic or specific and new growth. In the varieties of nonunion the author gives delayed union from mere cellular inactivity and definite nonunion from fibrous union (fibrous tissue or fibrocartilage between and connecting the bone ends); nonunion from pseudoarthrosis (bone ends eburnated and covered with fibrocartilage, a joint cavity with capsule and synovial fluid between the ends of the bones); nonunion from gap fracture (a piece of bone lost, the bone ends held apart by the companion bone). The bone is usually thin and atrophic. In the nonoperative methods the author writes on voluntary movements, the fracture being protected with a splint; second, on passive congestion with massage; third, on injection of blood or blood products in and around the fracture. Open operative treatment is advised whenever union has been delayed for more than twelve months, or when there is increasing mobility between the fragments associated with a Roentgen-ray picture of rounded bone ends separated by a definite gap. Methods of stimulating the bone ends are discussed. Shaping and fitting operations are given. The author finally states that the ideal and obvious method of treating ununited fractures is by putting in a bone graft. The causes of failure in this procedure are inadequate contact of bone ends, inadequate fixation of the fracture either by a constructive operation, graft or splint, inadequate splinting of the limb after operation and excessive tension.

Neoplasms of the Blood Lymph-vascular System.—PULFORD (*Ann. Surg.*, 1925, **82**, 710) states that a histologic study of the neoplasms of the blood lymph-vascular system of 290 patients treated at the Mayo Clinic shows 183 angiomas, 9 angioendotheliomas and 8 endotheliomas. This simple classification seems adequate to meet all the clinical facts of the cases as well as all the known data from the standpoint of embryology, morphology, situation and "reserve-cell" diagnosis. Endothelium in the embryo is derived from mesenchyme. In adult tissues, although not yet identified, the same mesenchymal cell lying invisible seems most likely to be the reserve cell of endothelium. Endothelium is closely linked with fibrous connective tissue in that mesenchyme is their common ancestor. This relationship does not preclude the existence of a specific tumor of endothelium, distinct from a fibrosarcoma. The study of angiomas led to the recognition of the origin of the malignant tumors of this series from vascular endothelium. A case reported shows the change from benign to malignant in different stages. These original hypotheses seem established as facts: Blood-vascular and lymph-vascular angiomas, while usually benign, are potentially malignant endotheliomas. There is an intermediate stage between these two represented by the angioendothelioma, which is relatively benign, but definitely malignant, and malignant endotheliomas of the blood lymph-vascular system exists as a pathologic entity.

Administration of Iodin in Exophthalmic Goiter.—RIENHOFF (*Bull. Johns Hopkins Hosp.*, 1925, **37**, 285) says that iodin produces definite and striking changes in the histologic structure of the thyroid gland in cases of exophthalmic goiter. These changes were: Increase in size of the thyroid gland as a whole, decrease in vascularity and probably in the lymph flow through the gland, a large increase in amount of fibrous connective tissue, a striking increase in amount of colloid deposited and contained within the thyroid gland, a change in the acini from lacelike papillomatous ingrowths to round, even-walled, smooth acini, regular in size and form, and the presence of many mitotic figures before the use of iodin and their absence after the iodin has been given. The clinical improvement and the lowered rate of basal metabolism are directly associated with the change from a typical histologic picture of exophthalmic goiter to a resting colloid stage. In comparing the histologic structure of the thyroid gland in 30 cases of exophthalmic goiter, 15 in which iodin had been given and 15 in which no medication whatsoever had been used, it was observed that the histologic picture following the administration of iodin was constant. An artificial remission of signs and symptoms is produced by iodin. A remission in a case of exophthalmic goiter is associated with a change in the histologic picture from a hyperplastic to a colloid state, even though there is definite evidence of hyperplasia remaining. It is a question of relative hyperplasia.

End Results in Neurosurgery.—SHARPE (*Ann. Surg.*, 1925, **82**, 684) writes that his impression of the end results, from the standpoint of the ability of the patient to earn a living and to be a useful member of the community has been discouraging, and particularly is this true of those patients having had lesions of the central nervous system, such as brain tumor, brain abscess, chronic brain injuries and internal hydrocephalus, whereas more encouraging results have been obtained in the operative treatment of trifacial neuralgia, lesions of the spinal cord, bronchial plexus and of the peripheral nerves, external hydrocephalus in its milder forms, chronic brain injuries of supracortical hemorrhage and then, possibly the most gratifying of all, the treatment of acute brain injuries both in the newborn and in adults. The factor of better teamwork between the neurologist and the surgeon is making possible earlier diagnosis and more accurate localization of the lesion. The surgeon knows what can be done and what cannot be done safely, and in this manner the catastrophies of the past are being avoided. The highly discouraging field consists of brain tumor, brain abscess and the condition of internal hydrocephalus. Fortunately the encouraging field consists of the larger number and of the more frequent neurologic conditions amenable to surgery. The older the patients at the time of the intracranial hemorrhage, the less marked are the gross physical and mental impairments, but the more marked are the subjective complaints, such as headaches, dizziness, early fatigue and changes of personality and the greater are the emotional and psychic impairments. The ideal time for the treatment of brain injuries in both infants and adults is at the time of the acute condition, when the intracranial hemorrhage can be drained.

PEDIATRICS

UNDER THE CHARGE OF

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Should the Schick Test be Abandoned?—KELLOGG (*Am. J. Pub. Health*, 1925, **15**, 868) made observations that showed that the Schick test is subject to many errors in its application, that more than offset the value of the information derived from its use. A high percentage of false negative Schick tests has been found in persons following immunization, the information as to their true status having been determined by laboratory tests using the Kellogg method. The Schick test is of academic interest only, and should be abandoned completely, for the following reasons that the author gives: It is subject to a sufficient percentage of false negative readings to result in the failure to protect children who otherwise would have been protected. Knowledge of the immune status of children is not required, as most of the age groups most concerned are susceptible, while immunization of the balance is open to no objection. General immunization of children without further attention as to whether they have been immunized or not will result in complete public health control of diphtheria. For determining the immune status of individuals and small groups, where this information is especially desired, the laboratory test devised by the author is convenient and accurate.

Therapeutic Results with Concentrated Scarlet-fever Antitoxin.—DICK and DICK (*J. Am. Med. Assn.*, 1925, **85**, 1693) state that the scarlet-fever antitoxin may be refined and concentrated by the method used in the concentration of diphtheria antitoxin, with an increase in potency and a reduction in serum reactions. In the concentrated and standardized antitoxin the disadvantages of the antistreptococcic serum have been overcome. The basis of the standardization of the antitoxin is the skin-test dose of toxin. It has been found that 1000 skin-test doses of toxin is an amount capable of producing transient symptoms of mild scarlet fever in susceptible adults, if given without any previous immunization. An amount of toxin sufficient to neutralize twenty times this quantity of toxin has been found to be an effective therapeutic dose. Since it is undesirable to inject large quantities of even refined serum, a minimum potency requirement has been established. This requirement is such that one therapeutic dose shall not exceed 20 cc. in volume. The prophylactic dose should be one-half of the therapeutic dose. Smaller amounts may protect moderately susceptible persons, but highly susceptible persons require the larger prophylactic dose for complete protection. The antitoxin is put out in therapeutic and in prophylactic doses. The authors inject the material into the muscles on the anterior aspect of the thigh. They feel that the time saved by intravenous injection of the dose does not compensate for the increased danger. In early cases the

rash is the most convenient indicator of the action of the antitoxin. If enough of the antitoxin is given the rash will be definitely faded within twenty-four hours, and there will be a marked improvement in the general condition of the patient, especially noticeable in the most toxic cases. The improvement will be associated with a fall in temperature. Following the removal of the toxic elements of the disease, the subsequent course of the temperature will depend on the presence or absence of complications. One effect of the antitoxin is the unmasking of such complications as already exist, making their recognition and proper treatment more certain. Of the 34 persons with positive skin tests and scarlet-fever streptococci in their throat cultures, following direct exposure to scarlet fever, who were given one prophylactic dose, 14 had sore throat and fever at the time the antitoxin was given. In 4 a rash was just beginning to appear. None of these 34 susceptible persons already infected with scarlet-fever streptococci developed scarlet fever. They also did not develop any complications. These results indicate that the prophylactic use of scarlet-fever antitoxin in sufficient amounts protects even after the infection has occurred. In the 64 cases of scarlet fever in which one therapeutic dose was given on the same day that the rash developed, no further administration of antitoxin was required. The rash was definitely gone, and the general condition was improved within twenty-four hours. Otitis media occurred in 1 case. No other complications or sequelæ developed in these patients who received antitoxin on the first day of the rash. Otitis media occurred in 5 of the 59 patients who did not receive antitoxin until the second day of the rash. Mastoid infection followed in 1 of these cases of otitis media. No postscarlatinal nephritis occurred in any case in which the antitoxin was given early. Antitoxin was not given after the third day of the rash to any but those patients who had become progressively worse during the first days of the disease, and were not seen until the end of the first week of illness. With one exception, all the deaths in the antitoxin series occurred in persons who had been ill from six to ten days before the antitoxin was administered.

Respiratory Catarrh in Children.—CLARKE (*Lancet*, 1925, ii, 864) noted that half of the children that he examined in routine examination had respiratory catarrh. These infants were from three to six weeks of age. He thinks that the development of respiratory catarrh probably depends on these two factors: The number and virulence of the catarrhal organisms which attack the mucous membrane, and the local resistance of the mucous membrane and the general immunity of the body. It has been shown that the mucous membrane secretes a definite bacteriolytic agent. It would seem from clinical observation that the very young mucous membrane is deficient in resistance, and that mucous membrane that has been the object of early and repeated attacks either loses or never acquires an adequate resistance. The mother and the germ-laden atmosphere are the sources of infection. To prevent infection, if the mother has acute catarrh when the baby is born, she should be instructed to wear a folded handkerchief over the mouth and nose while attending or feeding the baby. This precaution should be extended to the maternity nurse and children's nurse. All

persons coming in contact with the infant should be requested not to breathe on or kiss the baby. To avoid the other main method of infection, the germ-laden atmosphere, is an easy matter in an uncrowded house. The infant should either be kept outdoors or in a draft. It is difficult to overcome predjudice in this matter, especially during the daily bath, but the author says that it is certain that no infant can come to any harm if efficiently bathed in front of a fire with all the windows open. Children should be kept away from people with colds, and children's parties should be cut down to a minimum.

DERMATOLOGY AND SYPHILIS

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Treatment of Ulcus Molle and Serpiginosum.—In discussing a paper by Gross which mentions the very satisfactory results obtained by the use of Paquelin's cautery in this very resistant condition, BUSCHKE and LEISSNER (*Dermat. Wchnschr.*, 1925, 80, 544) praised particularly the curative results obtained with solutions of pyrogallic acid in gradually increasing concentration which was effective in one of their cases, even after every other method had failed. The concentration of pyrogallic acid may be gradually increased until the pure acid is used. Late and highly resistant cutaneous syphilids may be successfully treated by this technic. It is interesting to note that no Ducrey bacilli could be found in the lesions studied by the authors. The pronounced factor of individual resistance was well illustrated in one of their cases, in which the woman by whom the male patient was infected had a small chancroid which healed rapidly, while the patient himself developed the highly resistant and extensive serpiginous lesion.

Histopathologic Changes in the Central Nervous System in Pemphigus.—SCHREINER (*Dermat. Wchnschr.*, 1925, 81, 1559) reviews briefly the three groups of theories as to the etiology of pemphigus: The infectious theory, the bacterial intoxication theory and the autointoxication or metabolic theory. A number of authors have recently concerned themselves with metabolism and blood changes in pemphigus, and Eppinger in particular has found in 3 out of 6 cases changes in the spinal cord. He felt, however, that these could not be regarded as necessary associates of the disease process. Kraus and Huber detected changes in the brain as well as in the spinal cord. Bargum observed isolated changes in the peripheral nerves, but none in the spinal cord.

The author states that his observations are comparable to those of de Crinis, who studied particularly the alterations of the nervous system in severe metabolic disturbances, including particularly diabetes, eclampsia, epilepsy and experimental acidosis. Abnormalities in the staining qualities of the lipoid substance in the nerve tissues and morphologic changes in the glia and ganglion cells were observed. In the author's case of pemphigus Nissl preparations from the cornu ammonia showed an increase in the number of glia cells with regressive nuclear changes. The ganglion cells showed definite signs of disintegration. In other preparations it was possible to demonstrate a marked increase in glia fibers with lipoid droplets in the ganglion cells. The author takes the conservative view that a considerable series of studies will be necessary to establish the connection between such changes and the general pathology of pemphigus.

Observations on the Pharmacology and Toxicology of Bismuth.—HECKELMANN (*Dermat. Wchnschr.*, 1925, 80, 546), in discussing this topic, states that bismuth line in the gums is observed in 27 per cent of hospital patients and 8 per cent of those in private practice, and stomatitis occurs in 10 per cent of hospital patients as compared with 4 per cent in private practice. The discoloration is due to the formation of bismuth sulphid from the combination of the metal with hydrogen sulphid produced by bacterial decomposition in the mouth. A fatal case of grave stomatitis has been reported by Smechula and a second by Criado. In order to prevent renal complications Felke advises that if 0.3 to 0.4 gm. have been given in ten to fourteen days an interval of two weeks be allowed to elapse before the drug is resumed. No renal irritation is likely to appear until the total dose exceeds 1 to 1.5 gm. Betz has observed that the hematopoietic effect of bismuth is very similar to that of mercury. Erythrocytes decrease after the first injections gradually to 3.1 million and then gradually increase. The hemoglobin may diminish as much as 25 per cent, but again gradually rises. There is an early neutrophilic leukocytosis. The author cites a case of apparent idiosyncrasy on the part of the heart to the use of bismuth reported by Görl and Voigt, in which profound cardiac anxiety, tachycardia and irregularity with prolonged depression, sleeplessness and headache followed a single dose of 0.4 gm. Among the cutaneous complications a purpuric erythema is reported with severe stomatitis and recovery. The blood picture in this case is not described.

Bleeding Time in Socalled Diathetic Eczema.—In five comparable cases of chronic relapsing eczema in adults in whom the disease had been present since childhood, DESCHWANDEN (*Dermat. Wchnschr.*, 1925, 81, 1499) reports that there was a striking increase in bleeding time, averaging 56.8 minutes as compared with 36.4 minutes normal.

Chromolytic Studies of the Spirocheta Pallida.—To the very interesting problem of the organic constitution of the Spirocheta pallida MÜHLPFORDT (*Dermat. Wchnschr.*, 1925, 81, 1531) applies the methods of microchemistry, with particular reference to the attack upon it with the aid of dyes. His conclusions are substantially as follows: The Spirocheta pallida has a very complex chemical structure in which the

most important single item is a lipoprotein (confirming the findings of Schumacher). There are, however, no free lipoids in the Spirocheta pallida. In addition to the above-mentioned lipoprotein, chromolytic study of the organism shows that it consists of an outer layer of an acid-containing protein (containing nucleinic acid in an albuminous combination) and a basic protein substrate. No peroxydase could be detected. Any dye which will react chemically with the foregoing elements can stain the Spirocheta pallida. In particular Victoria blue 4 R is able to stain the lipoprotein, and the same property is inherent in other basic triphenyl methane dyes. The particular group in the triphenyl methane dyes which reacts with the lipoprotein is the phenyl radical. The Giemsa stain acts upon the albuminous material. The reaction to 3 per cent aqueous methylene blue takes place with the oxygen-containing acid protein combination. The only acid dye which will react directly with the Spirocheta pallida is a concentrated aqueous solution of erythrosin.

Relation between Verruca Vulgaris and Acuminate Condylomata.—BRANDES (*Dermat. Wchnschr.*, 1925, **81**, 1583) found that 68 per cent of a group of patients who had acuminate condylomata likewise had common warts on the hands, face or feet. The author believes that pointed condylomata have no necessary etiologic relation to gonorrhea. He reviews elaborately the literature demonstrating the autoinoculability of verruca vulgaris. This is paralleled by the review of the literature dealing with the autoinoculability of the pointed condyloma. From the collected observations a very fair case is made for the homology if not the identical etiology of the two processes.

The Odor of Arsphenamin.—LEIBHOLZ (*Dermat. Wchnschr.*, 1925, **81**, 1602), in discussing the observations of Thurzo on the odor of ether observed by patients receiving arsphenamin and neoarsphenamin, especially the latter, states that the dissolving of neoarsphenamin in water at blood temperature will do away with the odor in the majority of cases. He concedes, however, that there is an element of individual idiosyncrasy over and above the possible ether content of the arsphenamin which must be considered in such cases.

The Action of Arsphenamin in Tabes and Paresis and the Abortive Treatment of Syphilis.—SCHUMACHER (*Dermat. Wchnschr.*, 1925, **81**, 1404) discusses the theory that the failure of arsphenamin to reach the nervous system is due to its insolubility in lipoids. The most interesting detail of the presentation, however, is a condensed summary of the recent literature on superinfection in syphilis in its application to the curability of the disease. Kolle found that it was impossible to produce radical cures of syphilitic rabbits later than ninety days after infection, and that most of the successful cures fall within the first forty-five days. Buschke and Gumpert, Steinfeld, Frei, Brown and Pearce have demonstrated the possibility of superinfection in the rabbit. Buschke and Kroo, in studying the infection of rats with relapsing fever demonstrated the possibility of reinfection in these animals when organisms from the original infection could still be found in the brain. The author concludes that early syphilis is curable with

arsphenamin in man until it has invaded the nervous system. Once this involvement has taken place the inaccessibility of the organisms due to the lipoid insolubility of arsphenamin is such that relapse must be expected.

GYNECOLOGY

UNDER THE CHARGE OF
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Roentgenotherapy of Uterine Cancer.—BURNAM and NEILL (*Radiology*, 1924, 5, 1) have recently published a brief review of their experience in the treatment of cancer of the cervix and uterine fundus. Considering first cancer of the fundus, they divide this into three groups, namely: Early, or that in which the uterus is of normal size or slightly enlarged, with no evidence of metastasis; borderline, where the uterus is definitely enlarged with possible lateral thickening without fixation; advanced, where the body of the uterus is a fixed mass in the pelvis and metastasis is evident. In the early cases of this group they advise abdominal hysterectomy unless there is considerable vaginal relaxation, when vaginal hysterectomy, especially in older patients, is desirable. An exception should be made when the patient is old or suffering from some organic disease, making the operation or anesthesia dangerous. In such a patient intrauterine radiation up to $2\frac{1}{2}$ gm. hr., treating the entire uterine cavity, is a curative procedure, especially when the disease is limited to the endometrium. For this they use radium emanation. If after two months there is still discharge, the patient should be examined with a curet, and if diseased is retreated with about one-half the original dose. In the borderline cases they strongly advise abdominal hysterectomy; efficient radium application is difficult to attempt, and on account of the size of the uterus the mechanical difficulties of the vaginal hysterectomy are very marked. When operation is contraindicated for any reason, intrauterine radiation of 3 gm. hr. or more, combined with external through-and-through treatment, is indicated, and in a number of cases has yielded great improvement in the patient's health and both bleeding and discharge usually cease. These patients may, after such treatment, live for years in comfort. Rarely can one expect the disappearance of the mass, although it is not uncommon to find no evidence of growth by diagnostic curettage after the treatment. If operation should be decided on later the radium treatment will not make it more difficult than in ordinary cases. In the advanced cases of this group treatment should be palliative only; intrauterine treatment from 1 to 2 gm. hr. combined with moderate external radiation is given. No attempt is made to radiate organic metastases in other

parts of the body unless they are so located as to cause pain. By this method hemorrhage can be controlled, pain relieved and life prolonged. Considering cancer of the cervix, the authors believe that in the early cases the line of procedure is less clear than in the early body cases. It would seem that almost as many patients are curable by radiation as by operation, but it is not clear what advantage the combination of the two methods gives. It is logical to combine them and best as preoperative radiation, but, except for the fact that we do have some recurrences locally in previously healed cases, the radiation should be discontinued, as it is fraught with considerable danger and is not to be dissociated from morbidity and a marked mortality. Early cases, however, if good risks, should have a small primary death rate, but patients presenting serious organic complications should be radiated and not operated upon. They believe the best time to operate is during the week of the treatment, preferably the very next day, so that there will be no increase in technical difficulty. On the other hand, if operation is delayed there is a definite sclerosis of the tissues making the operation much more difficult. They prefer the abdominal operation, and do not hesitate to implant radium emanation points if the glands are found involved. They do not believe in postoperative radiation with radium unless there is vaginal or local pelvic recurrence. In the borderline cases it is probable that there will be a more general combination of surgery and radiation than in the early cases. If it is found urgent that these cases be radiated, to meet an emergency at the time of operation it is done by the implantation of emanation. They use the radium on a flat applicator, and in neither the early nor the borderline cases do they advise implantation of the parametria through the vagina. Where radium alone is used they give $3\frac{1}{2}$ gm. hr. in a single treatment. They prefer the single dose to the broken dose, as it seems to give very little upset, admits of much more accurate placement and takes less radiation. The second treatment is not to be considered under eight weeks, and only then if there is a definite new development beyond the site of the original disease.

New Method of Sterilization of the Female.—All the previous operative methods for the performance of sterilization of the female have required a laparotomy with the danger that necessarily accompanies such a procedure. Moreover, if it later becomes desirable to reëstablish the possibility of conception a second abdominal operation must be performed. To overcome such drawbacks a new method of sterilization has been proposed by HAENDLY (*Zentralbl. f. Gynäk.*, 1925, 49, 2404). The method depends upon the formation of a double vagina, and is carried out somewhat in the following manner: Long incisions are made through the vaginal mucous membrane on both sides of the cervix, beginning at the level of the os and running down to the vaginal inlet, ending about $1\frac{1}{2}$ to 2 cm. behind the urethral orifice. The vaginal mucous membrane is dissected free anteriorly and posteriorly to such an extent so that the flaps can be brought together in the midline without too much tension. An oval incision is made on the posterior wall of the cervix and the edges of this incision are sutured on each side with the edges of the anterior vaginal flaps, so that the cervix is united with an anterior vaginal canal. The posterior vaginal flaps on each side are then united to each other, thus making a second vaginal

canal behind the anterior one. The anterior canal, the orifice of which lies just under the urethral orifice and is so narrow that only a catheter can pass through it, serves as an exit for the discharges from the uterus and cervix. The posterior vagina, which is nothing more than a blind sac, is wide and serves the purposes of coitus. If, at a later date, it is desirable to reëstablish the possibility of conception, all that will be required is a long incision through this newly formed septum with suture of the edges on each side, thus reëstablishing the original vagina. The operation can be performed under local anesthesia, which is a big point in its favor, because it must often be performed on patients who are suffering from heart or lung disease and who ordinarily might not stand the danger of an operation.

New Round-ligament Operation for Uterine Retroversion.—New round-ligament operations, like the poor, are always with us, and it would indeed be a rather dull year that the gynecologic literature did not record a half dozen or more "new" operations of this type. However, once in a while, we feel that we must call attention to one of these operations so that we shall not be accused of being too conservative. The operation described by CARRINGTON (*Surg., Gynec. and Obst.*, 1925, 41, 507) consists of dividing the round ligament between ligatures at a point about midway between the uterus and the internal ring. A small incision is then made in the rectus sheath and another in the anterior leaf of the broad ligament below the division in the round ligament. Then, as in the Simpson operation, a clamp or pedicle needle is passed through the incision in the rectus sheath, carried extraperitoneally to the incision in the broad ligament, is then attached to the free end of the upper half of the round ligament, and on being withdrawn it pulls the round ligament to the rectus sheath, where it is sutured. The distal portion of the round ligament in the lower pelvis is then slid over the proximal portion, care being taken not to strip back the broad-ligament peritoneum from the round ligament. The free end of the distal half of the round ligament is then sutured to the anterior surface of the uterus and the broad-ligament peritoneum attached to it also sutured to the uterus. The proximal and distal halves of the round ligament are then sutured together for the distance that they lie parallel and in close proximity to each other. The procedure can be varied by perforating the broad ligament and carrying the distal portion of the round ligament through the perforation and then suturing it to the posterior surface of the uterus, thus performing a sling operation, similar to the Baldy-Webster operation.

RADIOLOGY

UNDER THE CHARGE OF

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Further Obserations on the Roentgen Diagnosis of Bronchiectasis.—MOORE and MARQUIS (*Am. J. Roentgenol. and Radium Therap.*, 1925,

13, 545) classify bronchiectasis into three groups of arbitrary division. The linear type, the earliest stage and characterized by increase in the linear markings along the terminal bronchi, is usually localized in the lower lobes. This stage is easily overlooked. The second group is the cylindrical type, characterized by a more marked increase in density along the course of the bronchi, with the density fan shaped and interspersed with clearer areas. This type is most common. The third type shows sacculation and is the most advanced. Roentgenologically it is recognized by large pseudocavitations and a marked increase in fibrous elements of the bronchial tract. As in the second stage, drainage by forced coughing and lowering of the head immediately before examination greatly aids the roentgenologist. Bronchiectasis is seen more often now because of more thorough postmortem examinations, and its increased incidence following influenza epidemics, irritation of gases of warfare and fibrosis due to roentgenotherapy. The cough and expectoration are most common symptoms, but are often overlooked by the patient. In the absence of tuberculosis hemoptysis is a very common symptom of bronchiectasis. Although there is a wide divergence of opinion concerning the value of the roentgenologic examination, careful examinations, conservatism in reports and the collaboration of the roentgenologist and the internist have made the Roentgen-ray examination of the utmost importance in the diagnosis of bronchiectasis. Robertson, of the Mayo Clinic, has pointed out that a person suffering from bronchiectasis is a very poor risk for any procedure that necessitates the prone position for any considerable length of time, and this emphasizes the importance of the diagnosis of bronchiectasis.

Deep Roentgen-ray Therapy of Mammary Carcinoma.—The results of deep Roentgen-ray therapy in breast carcinoma, according to EVANS and LEUCUTIA (*Am. J. Roentgen. and Radium Therap.*, 1925, 14, 135), have been sufficient to establish this form of treatment as a valuable aid in the care of breast carcinoma. They find that the manner of dissemination is one of the most important factors determining the outcome of the disease. This dissemination may be by embolic invasion of the lymph vessels and glands and extension by continuity by way of permeation of the lymph plexuses around the primary lesion. In last stages there may be embolic spread by the blood stream. All operable cases should be operated first and then immediately (eighth to twelfth day) followed by intensive postoperative Roentgen-ray treatment. In the series of 65 cases treated by the authors there has been no recurrences within the area treated in those cases given postoperative radiation of sufficient amount. The treatment aims to cover all possible areas, bearing in mind the permeated cancer area surrounding the lesion, which in some cases may extend 12 to 16 inches from the focus. The dosage must be sufficient to injure the carcinoma cells without injury to the normal tissues, and care must be taken not to produce severe fibrotic changes in the intrathoracic structures. This optimum dose has been found to be 90 to 100 per cent S.U.D. The authors advise against "carcinoma-killing doses." Their method is to use the very penetrating "hard" ray which will allow a more homogeneous distribution of the rays in the

tissues exposed. In this way cross-firing becomes unnecessary. The treatment is not repeated unless there is a probability that not all the carcinoma was removed, in which case the suspected area is re-treated in three months and again a third time.

Irradiation in Cancer of the Cervix.—TAUSSIG (*Radiology*, 1925, **5**, 5) reports on 263 cases of cancer of the cervix of the uterus, where radium was used alone or in conjunction with surgery or Roentgen ray, and found that of a total of 100 cases of cancer of the cervix treated up to four and one-half years ago 8 patients are still living. Less than one-quarter, however, of the patients were considered operable or borderline. Radium was used in the form of the element (150 mg.) except for some emanations. Deep Roentgen ray has been used also since 1922. The dosage now being given is from 4000 to 4500 mg., of which at least two-thirds is beta-radiation, with needles or bare silver tubes. The best results have been obtained by giving the total dosage within six weeks, this to be divided into a larger initial dose of 3000 to 3300 mg., followed by a second dose of 1500 to 1800 mg. in four weeks. This has been applied by inserting 50 mg. into the cervical canal, in silver, 25 mg. in silver beneath it and 75 mg. in the form of seven needles encircling the tumor mass. Complications are becoming less common, but must be guarded against very carefully. Post-operative recurrences in the vaginal vault have an extremely grave prognosis. The author has found early operation after treatment to be inadvisable and prefers to wait four or five weeks after radiation. About three weeks after hysterectomy he has found it advisable to give 100 mg. of radium in silver, brass and rubber in the vaginal vault for fifteen to eighteen hours. The value of prophylactic treatment of deep Roentgen ray is as yet not known. In view of the possible transplantation of cancer cells as a result of needle implantation into a cervical cancer, the author lately has preferred to treat these cases primarily with a series of Roentgen rays, totaling 850 ma. minutes, followed by application of radium needles and tube, unfiltered, amounting to 3500 mg. The value of gland metastases treatments is of still questionable and probably at best only palliative. American cures, as shown by statistics, are less than European, which can be explained on several factors, but until cases reach the physician earlier, and less "timbering" is done by those not qualified to treat these cancers, there will not be much lowering of the high death rate from cervical cancers.

Roentgenologic Examination of Normal and Diseased Bronchi after Filling with Lipiodol.—LENK and HASLINGER (*Klin. Wchnschr.*, 1925, **32**, 1533) credit Americans with the first use of a shadow-producing mixture (barium sulphate in oil) for examining the bronchial tree. Yet the method was not widely employed until the French began using lipiodol. Its chief application is in examination for bronchiectasis, and results have been satisfactory. The authors think, however, that many published illustrations of saccular bronchiectasis are really normal cases in which the alveoli have been filled with lipiodol. To prevent filling of the alveoli those writers recommend introducing the medium into the larger bronchi through a rubber catheter, taking

care: (1) Not to anesthetize the smaller bronchi previously; (2) to have the patient breathe only lightly during injection; (3) to avoid high pressure during injection. Fluoroscopic examination is preferable to simple roentgenography. The authors note that lipiodol in the bronchi will be coughed out in a few hours, but if it enters the alveoli it remains for months, disappearing only by absorption. A further observation is the fact that the lipiodol often accumulates, even against gravity along the fissures apparently because of a favorable relation to the main bronchi. This fact might explain the very common beginning of certain diseases, notably pneumonia, along the borders of a lobe.

The Present Status of the Roentgen Treatment of Purpura Hemorrhagica by Irradiation of the Spleen.—In 1920 Stephan reported two cures of purpura hemorrhagica by Roentgen radiation, according to PANCOAST, PENDERGRASS and FITZ-HUGH (*Am. J. Roentgenol. and Radium Therap.*, 1925, **13**, 558), and since that time there has been much discussion for and against this treatment. They report 6 cases in which the results were found to vary considerably. All patients received one-fifth of an erythema dose, the technic being: Open field; skin target distance, 18 inches; voltage, 120,000; 5 ma. filtered through 5 mm. aluminum; time, ten minutes; given from ten days to three weeks apart. One case gave a toxic reaction in the first treatment only; 3 cases showed platelet count increase, whereas the others showed no change. Four cases showed clinical improvement, but some of these had received blood transfusion prior to treatment, and none can be classified as "cured." It is felt by the authors that in order to draw conclusions of value a large series of cases must be carefully studied, and the technic of the blood examination be very closely guarded from the many sources of error. Transfusion of whole or citrated blood has been beneficial, as has been intramuscular injection of whole blood, the benefit resulting probably from the protein shock. Splenectomy has given the best results to date, and it suggests the possibility of good results from "massive" irradiation, of which experiments are now being performed. The authors append to their article an abstract of their exhaustive bibliography of the literature concerning the effects on the blood of splenic radiation.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Syringomyelia in Association with Acromegaly.—Cases are cited from the literature and grouped: (1) Not true acromegaly; (2) doubtful

acromegaly; (3) genuine acromegaly. Another group of cases is mentioned in which changes around the central canal of the spinal cord were found in acromegalics, but without physical signs so far as was known. McBRIDE (*J. Neurol. and Psychopath.*, 1925, **6**, 114) presents two cases with definite acromegaly and syringomyelia. Previous work points to the supposition that acromegaly precedes the syringomyelia. A theory is presented for the association of the two diseases. It has been observed that splanchnomegaly sometimes accompanies acromegaly, and it is presumed that such may take place in the cord with selective action on the ependymal cells of the cental canal ending in a gliosis.

On Brains with Total and Partial Lack of Corpus Callosum and on the Nature of the Longitudinal Collosal Bundle.—A case history is presented by DE LANGE (*J. Nerv. and Ment. Dis.*, 1925, **62**, 449) of a child that died at five months of age, in which autopsy revealed total absence of corpus callosum. The brain is carefully described. The microscopic anatomy is compared with the anatomy of a normal brain of the same age. It is thought the brain without a callosum resembled a Simian brain in configuration. Literature and etiology are discussed. Persons without a corpus callosum usually have mediocre or less intelligence, though apparently normal persons may have some agenesis of this structure. Some of such cases seem to have been "short tempered." What part the corpus callosum plays in coördinated movements of both sides of the body is not fully established.

Effect of Organic Brain and Spinal-cord Changes on Subarachnoid Space, Choroidal Plexus and Cerebrospinal Fluid.—Sections from the malignant tumors of the meninges are presented by HASSIN (*Arch. Neurol. and Psychiat.*, 1925, **14**, 468) to show that the brain is not invaded by such tumors, but the pia or arachnoid continue to be infiltrated. In meningitis the inflammation rarely invaded the brain. In brain softenings lipoids are carried to the ependymal layer and perivascular spaces. In a section of the cord from a case of poliomyelitis hematogenous elements seem to have been carried to the central canal. A section from a case of solitary tubercle of the cord shows the dura involved in the tuberculous process. The course of the infectious process seems to have been toward the surface of the cord. The works of Weed and Foley are discussed. The author favors the theory that the cerebrospinal fluid comes from the brain and cord tissue and that the choroid plexus and the villi are organs of excretion.

"Word Blindness" in School Children.—Most of the material was collected by ORTON (*Arch. Neurol. and Psychiat.*, 1925, **14**, 581) at an experimental clinic held in Green County, Iowa. Among the children who were reported as dull, failing, or retarded, by their teachers, were a large number whose greatest disability was learning to read. Three of this group were especially studied, and 1 (M. P.) was admitted to the Iowa State Psychopathic Hospital. In all 142 grade and high-school pupils were studied, and 88 of this group were referred by teachers because they were considered deficient. Eighty-four of the 88 gave intelligence quotients ranging from 25 to over 120. M. P., aged six-

teen years and two months, had a mental age of eleven years and four months; intelligence quotient, 71 (by the revised Stanford-Binet test). He seemed to be intelligent along mechanical and nonverbal directions, but had the greatest difficulty in reading and writing compositions. When certain alternative tests were used in the Stanford-Binet test his mental age was thirteen years and ten months; intelligence quotient, 86. In the head aphasia tests he named objects presented, and recognized them readily, but when he had to pronounce the name of an object presented he hesitated and made many mistakes. Reading was labored and slow. Copying was difficult; writing to dictation was done well. In copying many neographisms were apparent, and in reading neologisms or distortions of a particular type were frequent. It was apparent that he could respond to training, but only slowly, and the training required was of a very special nature. Fourteen other cases who had difficulty in reading were studied. These often presented the difficulty of distinguishing a lower case p from q or b from d, or confused on with no, or not with ton. Some of them could read from a mirror image as well or even better than from the printed page. The case of a woman is cited who was considered different from her family and less intelligent. She was observed to spell her words and reverse the direction of her words. Some evidence is given to show that left-handedness is more frequent in people with such disabilities; also stuttering, which occurred in 3 of 15 cases studied, and some undefined speech defect was present in 4 others. Fourteen of the 15 were boys. They showed more than average motor incoordination. The author presents some evidence from old inscriptions to show that the tendency to read in either direction, that is, from left to right or right to left, was present. He says that our system of print, favoring right-handed people, causes the impressions which get to the right visual hemisphere to be ignored. In a few the impulses from the right hemisphere cannot be ignored, and thus reading or writing interferences develop when the stimuli are visual. Three definite visual areas of the brain are presented, namely: Visual perception, visual recognition and visual association. Bilateral destruction of the first two of these are necessary for word blindness, but unilateral defect of the last would produce a degree of word blindness. Interesting charts are presented. The author names this new disorder strephosymbolia. The psychiatric sequelæ of these disabilities are: (1) Contented apathetic disregard of handicap; (2) mild paranoid reaction toward teachers; (3) development of feelings of inferiority; (4) emotional blocking. Some efforts are being made to devise the best training methods for persons with such defects.

Epilepsy as Symptom of Disseminated Sclerosis.—Literature is cited which discusses this problem by WILSON and MACBRIDE (*J. Neurol. and Psychopath.*, 1925, 6, 91), presenting eight cases. The following clinical varieties are mentioned: (*a*) Epileptiform attacks (Jacksonian); (*b*) epileptic attacks (generalized convulsions); (*c*) with petit mal attacks; (*d*) with "epilepsia-partialis continua." The various theories of pathogenesis are discussed, but no autopsy material was presented. The authors favor the view that disseminated sclerosis may possibly cause epileptic phenomena by cortical irritation.

Reactive Gliosis in a Case of Brain Tumor.—FREEMAN (*Arch. Neurol. and Psychiat.*, 1925, 14, 649) discusses the enlargement of the hemisphere on the side of tumor as due to: (1) Increase in substance; (2) vascular disturbances; (3) reactive gliosi. The gliosis is apparently most marked near the tumor, but is usually present at considerable distance from the tumor. A brain with a tumor in the extreme left frontal lobe was studied. A special neuroglia stain (Cajal) was used. The neuroglia cells were counted in sections from several areas from both hemispheres symmetrically located. In every case the left hemisphere (side of tumor) had more neuroglia cells. The neuroglia cells nearest the tumor also showed hypertrophy.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Intranuclear Inclusions in Visceral Disease.—The presence of intranuclear bodies with specific tinctorial properties has been widely accepted as indicative of infection with a virus having special affinity for tissues of neural or ectodermal origin. VON GLAHN and PAPPENHEIMER (*Am. J. Pathol.*, 1925, 1, 445) report a case with an anatomic diagnosis of abscess of the liver, ulcerative colitis with hemorrhage, suppurative pleurisy, lobular pneumonia and bronchiectasis. Cells containing intranuclear inclusions were found in the bases of the colic ulcers, in the wall of the hepatic abscess and in the alveoli of the lung. The authors bring forward for consideration the possibility that viruses of this type may localize in tissues other than skin and central nervous system. They also suggest that the virus related to these inclusion cells was concerned in producing the lesions found in the colon, liver and lung in this case.

Progressive Alcoholic Cirrhosis.—HALL and OPHÜLS (*Am. J. Pathol.*, 1925, 1, 477) report 4 cases of early alcoholic cirrhosis. The history of all 4 patients revealed chronic alcoholism and alcoholism was the principal cause of death in 2 of them. In no case was the cause of death directly related to the liver cirrhosis. All 4 livers were above normal in size. Microscopically there was evidence of damage to liver cells, as shown by failure of nuclei to stain along with hyaline granules and vacuoles in the cytoplasm. Accompanying this was a marked infiltration of leukocytes, lymphocytes and young fibroblasts. Signs of regeneration of liver cells and bile ducts were evident in all cases. In no case was any organism demonstrated in the liver tissue. The authors suggest that the same toxic agent which caused the liver necrosis was also the stimulus for the proliferation of fibroblasts.

Observations on Focal Tuberculin Hypersensitiveness in an Infected Organ Previous to a General Sensitization—STEWART (*Am. J. Pathol.* 1925, 1, 495) investigated this subject by injecting 0.1 cc. of a saline suspension containing 2.5 mg. per cubic centimeter of living bovine tubercle bacilli in the right testis of a series of normal guinea pigs. On the second, third, fourth, fifth, sixth, seventh and eleventh days following this 0.1 cc. of a 5 per cent old tuberculin was injected into both testes and also intradermally. The following results were noted: (1) The infected testis reacted to the tuberculin before any reaction elsewere; this occurred within twenty-four hours and was manifested by a focal desquamation and degeneration of the tubular epithelium, cessation of spermatogenesis and a surrounding leukocytic infiltration; no skin reaction occurred and the other testis was normal. (2) On the sixth day the control testis showed some focal reaction to the tuberculin. (3) The intradermal test did not become positive until the eleventh day. Control animals injected with physiologic saline did not give the same picture.

Experimental Glomerulonephritis.—BULL, CLAWSON and HARTZELL (*Am. J. Pathol.*, 1925, 1, 247) claim that of the four types of renal disease found in man, namely: (1) Exudative interstitial nephritis, (2) nephrosis, (3) arteriosclerotic kidney and (4) glomerulonephritis; only two had so far been produced in laboratory animals. These have been the exudative interstitial nephritis and nephrosis. They experimented with rabbits and monkeys, using both hemolytic and nonhemolytic strains of streptococci. The streptococci were obtained from human lesions, were grown on blood agar about twenty-four to forty-eight hours, and suspensions made with physiologic salt solutions. Nonhemolytic strains were generally used, and injections were made intravenously. With the rabbits they were able only to produce a few cases of interstitial nephritis and a few of nephrosis. They also used 14 young rhesus monkeys and obtained 2 cases of severe nephrosis, 1 of acute interstitial nephritis and 1 of a glomerulonephritis. The kidneys in this last case were moderately enlarged, with slightly adherent capsules. The cortices were opaque and no markings were visible. The surfaces were finely granular. Microscopically most of the tubules showed a definite reduction in size, and those attached to damaged glomeruli showed a pronounced atrophy. Five to 10 per cent of the glomeruli showed epithelial crescents, and many showed fusions between the glomerulus and the outer layer of Bowman's capsule. Many glomeruli had part of the capillary network occluded by swollen endothelial cells, and there were a few examples of exudative glomerulitis. They conclude that they have been successful in producing glomerulonephritis in this monkey.

The Origin of the Mononuclear Phagocytes of Peritoneal Exudates.—The peritoneal exudates investigated by MCJUNKIN (*Am. J. Pathol.*, 1925, 1, 305) were produced by injections of india ink, trypan-blue solutions and whole rabbit's blood into the peritoneal cavities of normal rabbits, splenectomized rabbits and rabbits receiving intravenous injections of india ink. The exudates were examined on filmed slides made by the method for supravital staining of Pappenheim and

Simpson. The author describes three types of mononuclear phagocytic cells: The "hyaline" cells, with a variable affinity for neutral red; "rosette" cells, with neutral red in wreath form; "nonrosette" cells, with the dye granules scattered diffusely in the cytoplasm. To determine the origin of these he examined the tissues and organs from normal, trypan blue and india ink rabbits, first in fresh preparations supravitally stained and second in paraffin sections of supravitally stained tissues. He believes that the "hyaline" cells come from the vascular endothelium. The "rosette" cells arise from the reticuloendothelium of the lymph glands, while the "nonrosette" cells seem to have a double origin, coming from either the lymph glands or the endothelium of the bloodvessels.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Relationship of Hard Water to Health: II. Effect of Hard Water on Growth, Appearance and General Well-being.—MYERS' (*J. Infect. Dis.*, 1925, **37**, 13) studies showed that white mice on a diet of grains and a natural very hard water (520 parts per 1,000,000 of $CaCO_3$) showed no striking differences in growth or appearance from those on a similar diet receiving distilled water. White rats on a diet of bread, milk and yellow corn meal exhibited no marked differences. Young rabbits on a diet of oats, carrots and alfalfa and the natural hard water were about 30 per cent heavier at the age of forty-two days than similar rabbits on distilled water. A few dogs on a mixed diet and the natural hard water grew faster and had a better general appearance than similar dogs with distilled water. Two calves on a diet of milk, oats, corn and alfalfa and a moderately hard water (200 parts per 1,000,000 of $CaCO_3$) were 20 per cent heavier at the age of eight months than a similar pair which had received only distilled water. Several groups of chicks on a grain diet and the natural hard water gained from 20 to 40 per cent more during the first few months of life than did similar groups on a distilled-water intake. Distilled water to which had been added as nearly as possible the same salts as were in the natural hard water gave practically the same results with chicks as did natural hard water. The same was true of distilled water containing 400 to 100 parts per 1,000,000 of calcium carbonate and of distilled water containing 2000 parts per 1,000,000 of calcium chlorid. Distilled water containing 200 parts per 1,000,000 of Na_2HPO_4 increased the rate of growth of chicks as much as did calcium. Two hundred parts per

1,000,000 of NaCl had no effect on growth of chicks. On a synthetic diet containing the essential foods, and including cod-liver oil, chicks receiving distilled water grew at the same rate as those receiving the natural hard water, or distilled water containing $CaCO_3$ of $CaCl_2$. The urinary output of calcium and phosphorus in rabbits was apparently not affected by the salts in hard water. In no instance did animals on distilled water develop better than those on hard-water, but the reverse was true under several conditions.

Extraordinary Dormancy or Delayed Germination of Spores which have been Subjected to Heat.—The report by DICKSON and others (*J. Infect. Dis.*, 1925, **36**, 472) deals with a series of observations on the thermal death time and germination time of botulinus spores based on a study of approximately 37,000 sealed-tube preparations which have been under inspection for from twenty-eight to thirty-nine months after the spores were heated. The maximum dormancies recorded are thirty-seven months for spores which were heated and incubated in oil stratified broth, twenty-two months for spores which were heated and incubated in broth without oil and eleven months for spores which were heated and incubated in agar. The maximum survival times and the greatest dormancies were observed in tube preparations in which the spores were heated and incubated in broth medium which was covered with a thin layer of mineral oil. Attention is directed to the practical application of these facts to the preservation of foods.

A Plan to Establish in the United States a Morbidity Registration Area, That is, an Area for the More Complete Collection of Data Relating to the Diseases of Man—LLOYD (*Pub. Health Rpts.*, 1925, **40**, 1549) states that a comparison of morbidity rates from various communities is important if proper evaluation of data is to be made. To best accomplish this, reports must be made to a central sanitary authority and must include at least diphtheria, influenza, pneumonia, poliomyelitis, scarlet fever, smallpox, tuberculosis, typhoid fever and whooping cough. The reports would be checked from time to time by agents of the central coördinating unit. Requirements are suggested for specific diseases.

The Rat Proofing of Vessels.—GRUBBS (*Pub. Health Rpts.*, 1925, **40**, 1507) points out the desirability of rat proofing of vessels from the sanitary and economic points of view in order that food and drink may be made inaccessible and hiding and nesting places abolished: "(1) All foodstuffs, whether new or garbage, should be in rat-proof containers or kept within rooms devoid of rat harborage and into which rats cannot come from without. (2) All small inclosed spaces should either be abolished or, if this is not possible, should be blocked off by material impenetrable to rats at all points where a rat may get a foothold in order to gnaw through. (3) Large openings should be closed by screening or by doors or windows that fit and that are impenetrable to rats at gnawing levels, and they should be kept closed; all small openings should be permanently screened or closed." General specifications are given and illustrations are provided.

PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF DECEMBER 14, 1925.

Trichomonas Buccalis.—M. J. HOGUE (from the Department of Anatomy, University of Pennsylvania Medical School). The protozoan flagellate, Trichomonas, was first found by Donne in the human vagina in 1837. Since then it has been found in the mouth and in the intestines. These forms have been called Trichomonas buccalis, Trichomonas hominis and Trichomonas vaginalis, according to their source. Some investigators consider them as three distinct species, others as one or two species. More information is needed before this point can be settled. With this end in view the present work was begun. Trichomonas buccalis has been studied both culturally and microscopically and compared with Trichomonas hominis, the form found in the intestine of man. Both Goodey (*J. Parasitol.*, 1917, **9**, 537) and Ohira and Noguchi (*J. Exper. Med.*, 1917, **25**, 341) published short accounts of this form, and called it Tetratrichomonas buccalis. Since then Trichomonas has been established as the generic name, so the form in the mouth is known as Trichomonas buccalis. During the past year I have found Trichomonas buccalis in nine persons in the scrapings from the teeth near the gums. It is present in the upper and lower jaws of men and women, both whites and negroes. The strains isolated came from persons with histories of pyorrhea, gingivitis and abscessed teeth. It was cultured for over seven months, with more than 110 transfers. The cultures were discontinued during the summer months, though the organisms were in excellent condition at that time. The culture medium was a mixture of equal parts of sterile sodium chlorid solution (0.85 per cent) and sterile sheep serum water (1 part of serum to 3 parts of water). Tubes of this were enriched with a small amount of saliva. They were incubated at 30° C. The strains were compared as to their vitality, their thermal death point and their sensitiveness to hydrogen-ion concentration. Slight differences were noticed in the various strains. When Trichomonas buccalis was compared with Trichomonas hominis, the form in the intestine of man, it was found that they grew on a culture medium differing in the amounts of serum and kinds of serum used. Also that Trichomonas hominis thrived on Locke egg medium and ovomucoid medium, while Trichomonas buccalis grew slightly on ovomucoid and not at all on Locke egg. Morphologically, the most striking difference was that pointed out by Goodey and by Ohira and Noguchi, that is, Trichomonas hominis has a free flagellum at the posterior end of its undulating membrane, while Trichomonas buccalis has no free flagellum at this point. All the nine strains of Trichomonas buccalis studied had four anterior flagella. They also had mitochondria and neutral red granules.

The Influence of Change in Temperature on the Location of the CO_2 Absorption Curve of Blood and Serum.—W. C. STADIE, J. H. AUSTIN and H. W. ROBINSON (from the John Herr Musser Department of Research Medicine, University of Pennsylvania). In the study of the acid-base equilibrium of blood almost all investigations have thus far been conducted at some one temperature, and the interrelations of CO_2 tension, CO_2 content, oxygen tension, oxygen saturation, variations in fixed acids and bases, such as sodium, potassium, chlorids, phosphates and organic acids at one temperature, have been fairly well defined. The effect of change of temperature upon these interrelations has been less extensively investigated. The most important effects of change in temperature are: (1) Variations in the solubility coefficients of the gases in blood and serum; (2) variation in the dissociation constant of carbonic acid and, in consequence of this, variation in the relation between the ratio, $\left(\frac{BHCO_3}{H_2CO_3}\right)$, and the pH; (3) variation in the base bound by protein. This study is an investigation of the third of these variations. In normal serums or blood the base is bound by: (1) Strong acids, chiefly chlorid; (2) cell and serum protein, to an extent dependent upon the concentration and type of protein, upon the pH and upon the temperature; (3) approximately the remainder of the base is bound by carbonic acid as bicarbonate. Since in a given specimen of blood or serum (1) is constant and only (2) and (3) vary significantly with pH and temperature, and since (3) is dependent upon the base remaining after the requirements of (1) and (2) are satisfied, it follows that: (*a*) Variations in bicarbonate at varying pH but constant temperature can be used as a measure of change in base bound by serum and cell protein with change in pH; (*b*) that variations in bicarbonate at varying temperature but constant pH can be used as a measure of change in base bound by serum and cell protein with change in temperature; (*c*) that there is a certain change of pH for a given change of temperature which will keep the base bound by protein and hence the bicarbonate constant. We have found experimentally in the whole blood, separated serum and true serum of sheep and dog that the change in pH per °C. change in temperature between 20° and 38° at constant ($BHCO_3$) is from − 0.017 to − 0.023 pH. The effect of change of temperature is to shift the plot of ($BHCO_3$) against pH toward the alkaline side with fall in temperature without any consistent change in the slope of the plot. The relation of true serum to its whole blood is not changed so far as our experimental methods demonstrated. The figures stated express also approximately the change in pH of blood or serum as it undergoes change of temperature without change in total CO_2 content. This study is consistent with the observations of Stadie and Martin on the whole blood of man, and extends their calculations of the heat of ionization of cell proteins to serum proteins, indicating that the heat of ionization of both is of about the same magnitude.

The Permeability of the Mammalian Erythrocyte to Certain Ions, with a Description of Two Simple Methods for the Study of Hemolysis.—M. H. JACOBS (from the Department of Physiology, University

of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.). The mammalian erythrocyte is a very highly specialized type of cell. Among other differences between it and ordinary cells appears to be a free permeability to at least certain anions—a property of much importance in the transport of CO_2 by the blood. The present investigation represents an attempt to throw further light on this difference by contrasting, in certain solutions, the behavior of the erythrocyte with that of the egg of the sea urchin, Arbacia, which resembles it in swelling and giving up its pigment in strongly hypotonic solutions. The solutions employed were: (*a*) NH_4Cl of different strengths and pH, and (*b*) mixtures of CO_2 and $NaHCO_3$ of different pH and CO_2 tensions. In the case of NH_4Cl the osmotic effects with Arbacia eggs were found to be almost the same as those of NaCl and KCl; with erythrocytes they were entirely different. In the case of the CO_2-bicarbonate system, the effects on the Arbacia eggs depended much more on the CO_2 tension of the solution than on its pH as such; with the erythrocytes the reverse was true, the pH being the factor of chief importance. These results are entirely in accord with the view that the egg of Arbacia is relatively impermeable to all ions, while the erythrocyte is permeable to at least certain anions but not in general to cations. In carrying out the experiments on erythrocytes two methods were used which have a number of advantages and do not appear to have been hitherto employed. The first depends on the fact that in experiments on hypotonic hemolysis concentration and pH may be looked upon as two independent variables. In the method ordinarily used the pH is kept approximately constant by the buffers of the rather large amounts of blood added to the solutions, and the concentrations of the latter are made to vary. In the new method, which permits the use of much smaller quantities of blood, the concentration is kept constant and the pH is varied. A convenient solution for normal and pathologic human bloods is one composed of 4 parts of M/13 NaCl + 1 part of M/13 $NaHCO_3$. The pH is adjusted in steps of 0.1 or 0.2 from 6.8 to 8.0 by bubbling in an excess of CO_2 and then slowly removing it with a stream of air, phenol red being used as the indicator. The second method makes it possible to determine the point where hemolysis begins and to follow its course in very dilute suspensions of corpuscles. Its essential point consists in the use of an apparatus by which the thickness of the layer of the suspension which just permits the image of the filament of a carbon lamp to show is read off on a scale, which can then by simple methods be calibrated to indicate percent hemolysis.

The Effect of Hydrogen-ion Concentration on Swelling of Cells.—B. Lucke and M. McCutcheon (from the Pathological Laboratory, School of Medicine, University of Pennsylvania, and the Marine Biological Laboratory, Woods Hole, Mass.). Study of the changes in size in living cells resulting from changes in the composition of the fluid medium in which they exist is fundamentally important both for physiology and pathology. Many investigations of the swelling of non-living material, such as gelatin, have been made and inferences have been drawn, thought to be applicable to living-tissue cells. Erythrocytes, because of their convenient availability, have frequently

served as objects of this sort of study. But it seems definitely certain that results obtained with dead proteins cannot be transferred to living protoplasm, and erythrocytes, from the standpoint of structure, vitality and chemical composition, can hardly be regarded as similar to the majority of animal cells. We have sought to study the effects of acids and alkalies upon the volume of cells which, in structure and composition, more closely resemble tissue cells and which, in addition, can be made to exhibit a definite criterion of life—for only in a cell possessing this latter attribute can one discover whether or not the production of an effect is dependent upon damage to vitality. The cells chosen were unfertilized eggs of Arbacia; they are spherical and hence easily measurable; they behave as if surrounded by a definite membrane; their vitality can be approximately estimated by determining their response to fertilization. In one series of experiments various lots of eggs were subjected to changes in the reaction of the surrounding medium, a pH range of from 3.0 to 9.8 being established by the addition of HCl or NaOH to neutralized sea water. Living eggs did not undergo change in size; only after they were severely damaged, as shown by subsequent fertilization experiments, did swelling occur. Similar results were obtained when CO_2 and NH_4OH were used. Work by others has shown that erythrocytes swell immediately under conditions similar to those which we have tested; this result is interpreted to mean the passage of ions into the cell, with consequent increase in osmotic pressure and attraction of water, in accordance with the permeability of the membrane and the laws of membrane equilibrium as formulated by Donnan. Our experiments show an entirely different response to acids and alkalies on the part of Arbacia eggs, and indicate that as long as the cell is uninjured a "Donnan equilibrium," such as occurs in erythrocytes, is not established in the cells investigated by us.

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ORIGINAL ARTICLES.

THE MORTALITY AND END RESULTS OF SPLENECTOMY.

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Before recommending the removal of a diseased spleen the physician must satisfy himself (1) that cure by medical measures cannot be expected, and (2) that the prospects of cure by splenectomy are sufficiently good to make the operation worth the immediate risk to the patient.

My purpose in this communication is to analyze briefly, from the standpoint of operative mortality, the experience with 417 cases in which splenectomy was performed, and to comment on the after history of the patients as related to the value of the operation.

The spleen is a hemolymph gland which belongs to the reticuloendothelial system, and has three known functions. The first is to filter from the blood stream microörganisms and various toxic agents, which it destroys or sends to the liver for destruction or detoxication. The spleen's failure to function as a filter results in its enlargement, of which that due to malaria and syphilis and the chronic toxic splenomegaly of the splenic anemia type are characteristic. The second function is to produce white blood cells, one of the most important being the lymphocyte, without which there would be no healing of wounds or repair in the body. All of the white blood cells have defensive functions, especially the large mononuclear endothelial leukocyte. In cases of leukemia a malignant expression is manifested in the unlimited production

of white blood cells which have the power of oxidation through their nuclear activities, but are without function owing to the lack of cytoplastic control. The third function is to destroy worn-out or deteriorated red blood cells, in the process of which bile pigments are found. An unnecessary destruction of the red blood cells which produces the suboxidation of anemia is one result of excessive splenic activity due to an increase in the size of the spleen from whatever cause. A specific action of the spleen on red blood cells is seen in its destruction of red cells with increased fragility, as in cases of hemolytic icterus, and in the destruction of the blood platelets, which is characteristic of chronic hemorrhagic purpura. Possibly the large spleens in these two conditions, as well as in certain other conditions, are to some extent the result of "work hypertrophy."

Sufficient clinical experience is now at hand to demonstrate beyond peradventure that in a number of diseases which otherwise would prove fatal, removal of the spleen has justified itself by curing them.

The statistics of early splenectomy show that the mortality was formerly from 25 to 35 per cent. The number of cases not being large, it is fair to assume that the high death rate led to delay in operation, until the patient's condition grew so serious that splenectomy was more than justified as a last resort. A vicious circle was thus established in which the high mortality brought about a delay responsible for a still higher mortality. Operative methods in the early history of splenectomy left much to be desired, but better technique, of which Balfour's method[1] of splenectomy is a fine example, has greatly reduced the surgical death rate.

From April 1, 1904, to January 1, 1926, splenectomy was performed in this Clinic in 417 consecutive cases, with an average hospital mortality of slightly more than 10 per cent. All the deaths that occurred in the hospital, without regard to the cause or the time, are included. If one adopted the thirty-day rule, that is, considered that if death took place more than thirty days after operation without surgical complication it was not an operative death, there would be a marked improvement in these statistics; but, unless an arbitrary method of classifying mortality is adopted, the tendency is, unconsciously perhaps, to "improve" the statistics. Moynihan, speaking of comparative statistics, says: "Statistics can be made to tell anything, even the truth." Certainly the method of computing hospital mortality with operative mortality at least gives the worse side of the picture. In the following tabulation the cases are classified on a clinical rather than a pathologic basis.

[1] Balfour, D. C.: The Technique of Splenectomy, Surg., Gynec. and Obst., 1916, 23, 1.

SPLENECTOMY (APRIL 1, 1904, TO JANUARY 1, 1926).

Cause.	Cases.	Hospital mortality, cases.	Per cent.
Disease of the spleen due to infection and toxic agents	190	29	15.3
Abnormality of the white blood cells	50	2	4.0
Abnormality of the red blood cells	147	7	4.8
Splenic neoplasm	10	3	30.0
Surgical accident	10		
Indefinite and unclassified	10	1	10.0
Total	417	42	10.3

In the series of 417 cases splenectomy was performed in 190 for conditions the result of infections or toxic agents. The average mortality for this group was 10 + per cent. Studying these cases more in detail, it was found that there were 10 in which a greatly enlarged spleen was removed for chronic syphilis accompanied by profound anemia. Prolonged treatment had failed to obtain and maintain a cure of the syphilis. There was 1 death in this series. Spirochetes and syphilomas were found in most of the spleens, and often gumma in the liver also. These patients were promptly relieved of all signs and symptoms of syphilis as well as of the anemia, and have maintained good health.

Splenectomy was performed in 8 cases for tuberculosis of the spleen, with 1 death. Although it is altogether possible from what we know of tuberculosis that these 8 patients had tuberculous foci elsewhere, careful physical examination disclosed none, and the patients have all remained well. The one death was probably the result of surgical accident. While the spleen was being removed a tuberculous abscess of considerable size was ruptured with more or less soiling of the field. Instead of tying the vessels of the splenic pedicle separately, which would have been wise, I tied with a ligature on a needle, piercing a vein and probably carrying tuberculous material directly into a venous channel, since the patient died with generalized miliary tuberculosis.

There were 24 cases of septic splenomegaly in which splenectomy was performed, with 7 deaths. Again 1 patient died from general sepsis. In this case also a difficult pedicle was tied in a septic field by a ligature-carrying needle. The patients in this group all had active infection primary in other parts of the body, such as osteomyelitis and septic endocarditis, with the spleen greatly enlarged secondarily. It was hoped that by removing this extensive source of secondary infection the patient might be given an increased chance of overcoming the primary focus, and this occurred in some of the cases. However, all the patients with septic endocarditis died, either in the hospital or within a few months after dismissal.

Looked on as a whole, the picture of septic splenomegaly is discouraging. The hospital mortality of splenectomy is high and the

percentage of cures low. While this does not argue that splenectomy should be abandoned in this condition, it does imply that patients should be chosen for the operation with care, and that if possible, operation should be postponed until sufficient immunity is established to render it relatively safe.

While many enlarged spleens were removed from patients who had had malaria previously, in none could the plasmodium be discovered in the blood or in the splenic tissue, and these cases have therefore been classified under splenic anemia.

For splenic anemia splenectomy was performed in 114 cases, with 13 deaths. Analysis of the syndrome of splenic anemia suggests that the enlargement of the spleen primarily is due to infective or toxic agents, and one may assume that if the causative agent is a microörganism, it had been destroyed through natural agencies, since in these cases bacteria could not be cultured from the spleens removed. Yet the condition of the spleen with its thrombophlebitis, atrophy of the pulp cells, and widespread infiltration with connective tissue, was remarkably like that found in the spleens removed in the septic and the syphilitic groups. In each case explored the spleen was removed regardless of consequences. Some of the very large spleens were so adherent, especially up under the diaphragm, that enucleation rather than removal was necessary. Possibly the operation should have been abandoned under such circumstances, but who can tell? At least there were more triumphs than defeats, even in the terminal conditions.

In 2 of the earlier cases of splenic anemia the patients died from hemorrhage or shock as a result of hemorrhage, within forty-eight hours after splenectomy. We had not then sufficiently learned the two most important lessons in surgery: *See what you are doing*, and *leave a dry field*. With our present knowledge the mortality in this group should not exceed 5 per cent.

The fact that the liver is so often involved in secondary portal cirrhosis in the terminal Banti stage in these cases suggests that toxic agents collected or manufactured in the spleen and sent to the liver might be the cause of the diffuse deposit of connective tissue in the liver—as though the liver in its endeavor to encapsulate poisons which it was unable to detoxicate or eliminate, brought about the cirrhotic condition. Many patients of this group had ascites and edema of the lower extremities, and were generally in such condition that any operative procedure carried great risk. Because we have had a number of cures under these most discouraging circumstances the operation is justified, even at the expense of unpleasant operative statistics. When one sees patients with profound anemia, hemorrhages from the stomach, portal cirrhosis and ascites recover after operation and remain well many years, it takes more courage to refuse to operate than to operate.

The majority of the deaths which occurred in the hospital imme-

diately after operation were caused by progressive thrombosis from the splenic pedicle reaching the portal system or the superior mesenteric veins. Ten per cent of the patients dismissed from the hospital died within the next ten years from secondary hemorrhages, usually from the stomach.

The spleen was removed in 19 cases of primary portal cirrhosis, with 6 deaths, a high mortality. Perhaps as good ultimate results could have been procured more safely by procedures based on the Talma-Morison operation, with which we have had some satisfactory experience.

We were led to remove the spleen in cases of primary portal cirrhosis and secondary enlargement of the spleen by reason of the good results that followed splenectomy in the Banti stage of splenic anemia. It was thought that removal of the spleen not only would prevent toxic material from reaching the liver, but also would reduce the amount of blood in the portal circulation, thus relieving the load on the liver, and that the bed from which the spleen was removed would afford large areas for the development of collateral circulation.

In the clear-cut case of splenic anemia the enlargement of the spleen is noted long before symptoms of liver involvement develop, if at all. With primary portal cirrhosis, which evidently has its origin in toxic material from the gastrointestinal tract, enlargement of the spleen occurs late, and, as a rule, is much less marked than with splenic anemia. There are some cases, however, in which it is difficult to determine whether the gastrointestinal tract or the spleen is the primary source of the infection, and in a careful consideration of all the facts, splenectomy should be included. Certainly a number of these patients were greatly improved following splenectomy, have remained in good condition and are able to work. The high mortality and poor end results in this group of primary portal cirrhosis, as contrasted with those in the group of secondary portal cirrhosis of splenic anemia, are to be regretted, but when one considers the hopeless condition of the patients, and that several of the 6 deaths which occurred were delayed and had no direct connection with the operation, one derives some consolation if not satisfaction.

Splenectomy was performed in 15 cases of biliary cirrhosis, with 1 death. The type of biliary cirrhosis concerned is a curious condition in which chronic obstructive jaundice appears with a greatly enlarged liver and enlarged spleen, but without evidence of that infection of the gall bladder or common duct which accompanies the ordinary type of biliary cirrhosis so familiar in gall-stone disease. The gall bladder was not greatly distended, and did not show gross evidence of disease in any of these cases. The common duct was thickened in all cases, although in the cases in which it was opened and examined its caliber, as a rule, was not greatly

increased; thickening of all the bile ducts seems characteristic of the disease.

Some of these cases might be called Hanot's cirrhosis, if one could judge from Hanot's description just what was meant, and it is possible that some of the cases were atypical hemolytic icterus or were confused with it. Surveying the group as a whole, it is to be noted that the jaundice, unlike hemolytic icterus, was obstructive, that is, there was bile in the urine and the stools were clay colored. There were no gall stones, which are present secondarily in hemolytic icterus in 68 per cent of cases, without regard to the age of the patient. Again, in no case did the jaundice clear up completely, although it became less marked and occasionally indistinct, but the anemia disappeared, and most of the patients were able to return to their work.

The spleen was removed in 50 cases in which the splenomegaly clinically was concerned chiefly with the white cells, with 2 deaths. In cases of leukemia there is a pathologic increase in the production of white cells by all the reticulo-endothelial tissues. In splenomyelogenous leukemia the spleen is perhaps the chief source of the white cells, but not the only one. Forty of the 50 cases in which splenectomy was performed were of splenomyelogenous leukemia, with regard to which some interesting facts were developed. If the spleen is reduced by Roentgen ray and radium in such cases it can be removed without much risk. In all the cases immediately following removal of the spleen, which was greatly enlarged and burdensome, the white cells promptly decreased from an average of several hundred thousand to less than 100,000 and often to less than 50,000. Some of the patients have been able to continue their work and support their families for more than five years, although the blood has not become normal.[1] In most cases, however, after temporary improvement the disease pursued its fatal course.

In removing the spleen in cases that at first had been favorably affected by radium and Roentgen ray, but not later, it was noticed that the spleen had become greatly changed in its outer layers; changes which acted, so to speak, as a protective capsule around the active splenic substance, and the failure to secure better results from radiotherapy is probably due to this action.

In young persons in the early stages of splenomyelogenous leukemia, and especially in the atypical types, splenectomy is well worth consideration. Reduction of the size of the spleen by radium and Roentgen ray previous to operation is advisable.

In 4 cases the spleen was removed for lymphosarcoma, with rather surprising results. There were no deaths, although the spleens were huge, and the patients lived for considerable lengths

[1] This is much the most favorable report on splenectomy in leukemia with which we are acquainted.—ED.

of time. One patient, a young married woman with one child, lived nearly eight years, raised two children, and died from lymphosarcoma which had metastasized to the lungs.

In 1 case of enlarged spleen, which proved to be Hodgkin's disease, splenectomy was performed without particular benefit, and the patient died within the year.

There were 3 cases of lymphoma in which the very large spleen was removed with permanently good results.

For conditions caused by abnormalities of the red blood cells the spleen was removed in 147 cases, with 7 deaths. In such cases splenectomy is most effective.

Splenectomy was performed in 69 cases of hemolytic icterus, all showing more or less fragility of the red cells, which persisted after splenectomy, with 4 deaths. Two of the deaths it is difficult to ascribe to the operation. The 65 patients were cured and have remained well. Gall stones were present in 68 per cent, even in young patients.

The spleen was removed in 11 cases of hemorrhagic purpura, with no deaths. Before operation there was a reduction of blood platelets from a normal of between 225,000 and 400,000 to between 80,000 and 10,000, and while the platelets after splenectomy usually came up to normal or above, in some cases they remained below normal. These patients were all immediately relieved by the operation and have remained well.

The spleen was removed in 1 case of polycythemia apparently in the terminal stages. Although the spleen was unusually large, there was a remarkable restoration to health which has lasted for more than four and a half years.

There were 62 cases of pernicious anemia in which splenectomy was performed, with 4 deaths. The deaths occurred in the earlier cases in which operation did not appear to be justified until the condition of the patient was precarious. In the last 40 cases there were no deaths. The greater number of these patients were operated on soon after Eppinger made his classical report, and a period of four years elapsed in which we did not perform splenectomy for pernicious anemia. However, when Giffin studied the postoperative histories of these patients he found that comparable patients for whom splenectomy had been performed had lived two and a half times as long as those who had not been operated on, and some were alive and in fair health more than five years after operation. It is probable that some of the earlier cases classified as pernicious anemia were in fact cases of aplastic anemia, for which splenectomy is of no avail.

Among young patients otherwise in good condition and in the earlier stages of the disease, splenectomy is worth a trial in selected cases and especially in the atypical cases. One gets the idea that the spleen is not primarily concerned with pernicious anemia, but

that in the course of the day's work it destroys deteriorated red blood cells, which in pernicious anemia though deteriorated are still capable of maintaining life and are the best the bone marrow can produce. In no case did the blood return to normal after splenectomy.

Ten cases of splenomegalia were not classified from lack of sufficient knowledge as to the cause of the enlarged spleen, and it is probable that with increasing knowledge we shall find that a number of other cases have been incorrectly classified. In 20 cases the spleen was removed for splenic neoplasm and traumatism.

Summary. A survey of the foregoing experience demonstrates clearly that removal of the spleen is compensated for by the widespread tissues of the reticulo-endothelial system, of which physiologically it is a none too important part. The diseases with which the spleen is concerned are complex and pathologic processes are seldom primary in the spleen; it often acts merely as an agent of destruction.

From the surgical standpoint, it can be said that if a patient is properly rehabilitated and on the up-grade, the result of proper methods of preparation, the mortality of splenectomy will be less than 5 per cent. No patient should have the spleen removed for chronic conditions when he is on the down-grade, as we found out by bitter experience. The dangers of the operation are largely in delay and in an unfortunate choice of cases.

CONCERNING THE CONFUSION BETWEEN ACUTE LEUKEMIA AND INFECTIOUS MONONUCLEOSIS.

With the Report of a Case of Acute Lymphoblastic Leukemia with Remission.

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and

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Considerable attention has in the past five years been centered upon the similarity of acute leukemia and infectious mononucleosis one to the other and upon the differential diagnosis between them. Confusion still exists and threatens to become worse with the introduction into the literature of another somewhat similar syndrome under the name Agranulocytic Angina. The records of carefully studied cases of these conditions are needed and for this reason this review and case report are being presented.

The confusion which exists in this field finds its origin, as is so often the case, in bewildering terminology, mistaken translations and in the reports of incompletely studied cases. Several fundamental difficulties enter into the matter; the most important of which concern the classification and identity of the very different types of white blood cells which by various writers have been at times grouped under the loose heading "mononuclear."

A very brief survey of the literature makes it clear at once that under this term have been included the following: Lymphocytes, lymphoblasts (large lymphocytes, and so forth), myeloblasts, monocytes (large mononuclears, transitional cells, endothelial leukocytes, and so forth). No wonder confusion exists, especially when a writer in one language employs a term with one meaning and the translator in another. The second important source of confusion rests on the failure of many writers to distinguish between an actual and a relative increase of a given cell type in the blood. Many statements also are quoted incorrectly.

Let us start then by reviewing the terms to be employed and the conditions to be discussed.

I. The Cell Types Concerned. (*a*) The *myeloblast* is the only member of the granular or myelogenic series of white blood cells which could ever be included under the term "mononuclear" and is the most immature member of this series. For our present purposes this cell form may be said only to occur in the peripheral blood in leukemia; in small numbers in chronic myelocytic leukemia but in very large numbers in acute myelocytic or myeloblastic leukemia. In this latter instance the myeloblast must be distinguished from the corresponding lymphoblasts of acute lymphatic leukemia by the presence in the myeloblast of oxydase granules and of proteolytic ferment.

(*b*) The *lymphoblast* so closely resembles the myeloblast that special methods are required to distinguish them. It is the most immature form of the lymphatic series ever to enter the circulation and occurs in the largest numbers in acute lymphatic or lymphoblastic leukemia. All gradations between this cell and the mature lymphocyte of normal blood may be seen and in any condition of active lymphocytosis there is a tendency for younger, larger lymphocytes to appear in the blood.

(*c*) *Lymphocytes.* The mature lymphocyte is the small deeply staining lymphocyte of normal blood. Its younger forms are somewhat larger and have relatively more cytoplasm. In many reports these cells have been included under the term mononuclear only to have the figures quoted later in an article in which the term mononuclear was limited to the cells of the group next to be considered.

(*d*) *Monocytes.* These cells by some have been called endothelial leukocytes because of their endothelial origin, by others large

mononuclear cells and transitionals because they were once thought to give rise to the granular leukocytes (polymorphonuclear leukocytes). The term mononuclear has often been limited to that form of monocyte with the round nucleus and has also been used to include the form with the indented or kidney-shaped nucleus formerly called "transitional."

It is obvious that confusion will arise so long as the term mononuclear may be applied to any one or all of these forms. Mononuclear is not synonymous with monocyte nor can it be safely used at all unless defined in each case. It had best be dropped altogether from hematological literature. There is no need for the limited terms mononuclear and transitional; these can both be included under monocyte, nor is there any valid excuse for using the term mononuclear to cover the whole group of cells which happen to have a single unbroken nucleus.

Before proceeding a word should be said about simple lymphocytosis. Confusion has arisen through a failure to distinguish between a relative and an absolute lymphocytosis and through the inclusion of lymphocytes under the term "mononuclears." Relative lymphocytosis occurs with great frequency as a result of a neutrophile leukopenia and the emphasis should be placed on the primary reduction in the neutrophile count and not on the wholly secondary relative increase in lymphocyte percentage. The list of conditions usually given in which lymphocytosis occurs is largely a list of conditions in which neutrophile leukopenia is present. A disappearance of neutrophile and other granular leukocytes leaves behind only the lymphocytes and monocytes and this state of the blood has unfortunately often been referred to as a mononucleosis.

An actual lymphocytosis of any considerable degree occurs in but few conditions. In pertussis a total white count up to 85,000 may occur with even 95 per cent of mature lymphocytes, a picture which might well suggest chronic lymphatic leukemia. Crombie[1] has reported 2 cases of whooping cough in infants with much higher counts; one with 113,000 with 67 per cent of lymphocytes, the other with 233,000 total white cell count of which 58 per cent were lymphocytes.

II. *Conditions in which confusion arises as a result of changes in the white blood-cell picture involving the cell types just enumerated.* These include the following:

(*a*) *Acute Leukemia.* The predominant cells of the myeloblastic and lymphoblastic types of acute leukemia when stained with eosin-methylene azure stains can usually not be told apart and more study is required to identify the type of leukemia. There should be little or no confusion, however, between the blood picture of simple lymphocytosis or chronic lymphatic leukemia with that of acute leukemia in which the larger immature lymphocytes and lymphoblasts with more cytoplasm and less deeply-staining nucleus form

the greater part of a total count which as a rule rises well above 50,000 and often exceeds 100,000 per cm.*

(*b*) *Infectious Mononucleosis.*[2, 3] In this disease which may be identical with what was formerly called glandular fever, and which is usually or always associated with a Vincent's angina, there occur marked changes in the blood picture. Many of the cases, though not all, have a leukocytosis which occasionally exceeds 20,000, and is due to an increase of the cells of the lymphocyte series both mature, immature and perhaps abnormal. Often 70 or 80 per cent of the total number of white cells are apparently normal mature lymphocytes. At other times there are a greater number of larger cells which suggest immature lymphocytes or even lymphoblasts. It is these cells which lead to the suspicion of acute leukemia.[4]

The term mononucleosis as applied to this disease is unfortunate. Those who limit the term mononuclear to a type of monocyte will be misled into expecting an increase of these cells. Some term expressing the lymphocytosis would be preferable, several have been suggested, for example, acute benign; lymphoblastosis,[5] acute lymphadenosis.[4]

On the one hand the blood picture of infectious mononucleosis may be confused with that of acute leukemia and on the other hand with simple lymphocytosis. This will be discussed later.

(*c*) *Agranulocytic Angina.* A recently coined term to describe a condition of angina with leukopenia due to the disappearance from the circulating blood of all or almost all of the white cells belonging to the granular or myelogenic series, in other words, a neutrophile leukopenia with, of course, a relative lymphocytosis or as some would say "mononucleosis." The reported cases have most of them had counts well below normal, some as low as 900 per cm. with as high as 98 per cent lymphocytes; but in a few cases[6] reported under this heading the total count has been normal or even above normal for at least part of the illness. For example, one of Zadek's cases had a total count of 17,100, of which 86 per cent were lymphocytes. This case which perhaps was one of infectious mononucleosis recovered promptly, whereas the cases reported with characteristic leukopenia all die. One case reported by Moore and Wieder[7] recovered from her first attack in which the count fell to 1200, but succumbed to a second attack two years later.

Most of the case reports of agranulocytic angina have been from Germany,[8, 9, 10, 11, 12, 13] but a few cases have been reported elsewhere.[14, 15, 16, 17, 18]

It is immediately apparent that these cases resemble closely the picture presented by any overwhelming infection in which there occurs a neutrophile leukopenia. On the other hand, the few cases without leukopenia come closer to infectious mononucleosis and in Skiles' case Vincent's organisms were found in the angina.

* In the aleukemic or leukopenic stages greater difficulties are presented.

Discussion. The confusion in this field is of long standing and many aspects. For example, in 1907, Türk[19] saw a patient with tonsillitis and adenopathy, in whom the white cell count was 16,700 and the lymphocytes constituted 85 per cent of the number. Turk made the diagnosis of acute lymphatic leukemia and gave a bad prognosis. The patient recovered and in the light of our views today was probably a case of infectious mononucleosis.

It was from such cases that the statement of a lymphocytosis in septic infection arose, as Tidy[20] has pointed out. Many of the cases of so-called sepsis were probably infectious mononucleosis, others perhaps leukemia. Not one according to Tidy supports the statement of an actual lymphocytosis in septic infection. Marchand's[21] Case VI and Cabot's[22] Case XII both strongly suggest the picture of infectious mononucleosis.

Of course, relative lymphocytosis does occur in severe septic infection as a result of the neutrophile leukopenia and this also has led to confusion just as the same picture has in aplastic anemia, benzol poisoning and the other conditions in which there is a lessened bone-marrow activity. Insofar as the blood picture is concerned there is no difference between that of neutrophile leukopenia on the one hand and that of so-called agranulocytic angina on the other. That agranulocytic angina is said to occur chiefly in middle aged or elderly women is surely not distinctive and an insufficient number of bacteriological examinations are on record to permit any statement on this phase. The fatal outcome is in keeping with what would be expected in any infection overwhelming enough to reduce the count of circulating white cells to this degree. That the infection in so-called agranulocytic angina is chiefly in the throat and mouth does not influence the argument, but does help to cause confusion with infectious mononucleosis, scurvy and acute leukemia, especially if the latter be in the stage with little or no increase of white blood cells.

It is true that acute leukemia may be present for a time without any great increase in the white blood-cell count and during this stage the differentiation from infectious mononucleosis may be very difficult. Some believe that the differential diagnosis can be made from a careful study of the predominating type of cell,[4] but this is very difficult. Acute leukemia may occur at any age in either sex; infectious mononucleosis has been recognized most often in young males, many of them medical students, but it is probably a matter of the care of study of such cases. There is nothing about the glandular enlargement to differentiate the two conditions except perhaps the greater tendency for the adenopathy to be limited in infectious mononucleosis to the cervical and submaxillary glands. The discovery of Vincent's organisms does not settle the matter, but does create a hope that the condition is "infectious mononucleosis." Perhaps the total white-cell count

will first settle the diagnosis. No case of unquestioned infectious mononucleosis has been reported in which the total white cell count approached that usually seen in acute leukemia. By far the majority of cases of infectious mononucleosis have a white cell count below 30,000 per cm., while by the time a case of acute leukemia has definite adenopathy and a sore mouth the count is usually in excess of 50,000. Of course, aleukemic periods occur in the course of some cases of leukemia.

Anemia is a constant symptom of acute leukemia but has been present in only a few of the reported cases of agranulocytic angina (Zadek's Cases III and IV with 43 per cent and 29 per cent hemoglobin respectively). Anemia is not a part of the picture of infectious mononucleosis, but is very marked in aplastic anemia. Anemia, therefore, is of some diagnostic assistance.

The cause of acute leukemia is not known and there is nothing absolutely diagnostic about the mouth and throat lesions which occur in this disease. In these lesions many mouth spirillæ may be found, and Vincent's organisms may also be present, but there is no evidence that any of these organisms are the true cause of the disease. Vincent's angina has been reported in so many of the cases of infectious mononucleosis as to suggest that this syndrome is merely a reaction to this infection. Whether the agranulocytic angina may prove also to be due to Vincent's angina it is impossible to say. No mention of these organisms is made in most of the case reports. B. pyocyaneus was found in the throat lesions of several cases and from the blood in one. Such results are too few to draw any conclusions from.

In this brief review then it is made clear there exists confusion in the matter of cell types, in the terminology employed and in the differential diagnosis of these several syndromes. The following case is reported because it illustrates and helps to clarify some of these difficulties.

Case Report. F. R., male, aged twenty-one years, an American, was admitted to the Hospital of the University of Pennsylvania on October 30, 1924, complaining of continuous nosebleed and fatigue.

History of Present Illness. Two months ago he began to feel tired all the time. Four weeks ago he had "tonsillitis" and an eruption on the face which was said to have been "barber's itch." He recovered from this acute condition but continued to grow weaker and more fatigued. Six days ago there developed sudden epistaxis repeated daily, and sometimes lasting several hours. Dr. Thomas H. Llewellyn, who referred the patient to the hospital, diagnosed the case as Vincent's angina. In spite of treatment the bleeding continued, weakness increased and the patient fainted on the day before admission.

Previous Medical History. Unimportant.

Family History. Negative. No bleeding tendency in any relative.

Social History. The patient was a druggist. He took no drugs and had not been exposed to benzol. He used tobacco and alcohol moderately.

Positive Findings of Physical Examination (Dr. Schenck). The patient was pale and asthenic, dizzy and nervous. Blood oozed from the nose and there were petechiæ in skin of neck, trunk and extremities. The tonsils were enormous and hyperemic. There were some petechiæ in mucosa of the mouth, but no membrane or ulcers. There was slight enlargement of the submaxillary, submental, cervical, epitrochlear and inguinal lymph nodes. Hemic murmurs were heard over the base of the heart. The spleen was enlarged down to the level of the umbilicus. The liver edge could not be felt, but the liver was enlarged to percussion. Dr. Schenck's tentative diagnosis at this stage of the study of the case was: Acute lymphatic leukemia. Acute tonsillitis (symptomatic of the leukemia).

Laboratory Examinations. Urine analysis was unimportant; the phthalein test 55 per cent. Smears from the tonsils were negative for Vincent's organisms. Cultures showed streptococci of both hemolytic and non-hemolytic strains. The Wassermann test was negative.

Blood Examination. October 30, 1924. Hemoglobin 40 per cent; red blood cells, 2,100,000 per cm.; white blood cells 577,000 per cm. Differential count; Neutrophilic leukocytes, 0.7 per cent; eosinophilic leukocytes, 0.0 per cent; basophilic leukocytes, 0.3 per cent; myelocytes, 0.3 per cent; lymphocytes, 98.7 per cent and monocytes, 0.0 per cent. An oxydase stain confirmed this count; 98 per cent of the cells possessed no oxydase granules. Coagulation time of venous blood by Wright's method was 6.5 minutes. Clot retraction was abnormal, and failed to respond in six hours. Coagulation time of finger prick blood was one-half minute. Platelets numbered 239,000 per cu.mm. A tourniquet test was positive.

A study of the cells included in the above count under the heading lymphocytes showed them to range in size all the way from a small mature lymphocyte of normal blood to a much larger cell as big as the average myelocyte. In the larger cells the rim of cytoplasm was relatively greater and sometimes stained the light basophilic tint characteristic of the lymphocyte series, but in a few instances the cytoplasm had the deeper basophilic strain suggesting the irritation form of Türk. However, the entire group appeared to be lymphocytes and this is confirmed by the oxydase stain. It would seem quite proper to divide this group of lymphocytes into three headings: Mature lymphocytes, immature lymphocytes and lymphoblasts; but attempts to make such differential counts led to consider-

able confusion as the grading from one form to another was so gradual that it would require an arbitrary division. Myelocytes which were seen were mostly neutrophilic although an occasional eosinophilic myelocyte was found. The further course of the blood changes is shown in the charts on pages 328 and 329.

Diagnosis. These hematologic findings seemed to confirm the diagnosis of lymphatic leukemia. Such a high total count with such a degree of lymphocytosis is more common in chronic lymphatic leukemia than in the acute form, but the shortness of duration of the illness and a certain tendency of the lymphocytes to be larger and with relatively more cytoplasm than the usual mature lymphocyte argued strongly for the diagnosis of acute lymphatic or lymphoblastic leukemia.

Course of Disease. Although it was felt that the prognosis was almost hopeless, treatment was instituted as follows:

(*a*) Iron and arsenic hypodermically daily; (*b*) local treatment of throat with solution of silver nitrate; (*c*) blood transfusions; (*d*) neoarsphenamin intravenously.

At first there was but little improvement but soon very marked improvement occurred. The charts show the rapid drop in the leukocyte count and the correspondingly rapid improvement in the anemia. The number of transfusions and their amounts is noted in the charts.

Within two weeks after admission the patient's entire picture had changed. The bleeding had stopped, petechiæ and tourniquet test had disappeared, the patient's color had markedly improved and the spleen had lessened in size. The vision, which had been seriously impaired by retinal hemorrhages, had so far improved that the patient could now read. A very marked improvement in the retinal findings was noted by the consulting ophthalmologist, Dr. Thomas B. Holloway.

On November 15, there was a return of tonsillar ulceration and petechiæ, but this caused little or no setback in the steady progress of the case. There was, however, an increase in the size of the enlarged cervical and neighboring glands. The throat improved within three days. Examinations of material from the throat were all negative for Vincent's organisms.

A week later an earache developed and spontaneous rupture of the drum occurred with a small amount of discharge. It is interesting to note that on this date the red blood-cell count was over 4,000,000, the hemoglobin percentage 85, and the total white cell count 7100. Only the differential count revealed any abnormality, the high lymphocyte percentage persisting, 74 per cent of the total.

Another week of improvement passed. The spleen and lymph glands became smaller, the total white count dropped to 4800 and the ear condition subsided somewhat. At this time the change from the date of admission four to five weeks previously was amazing,

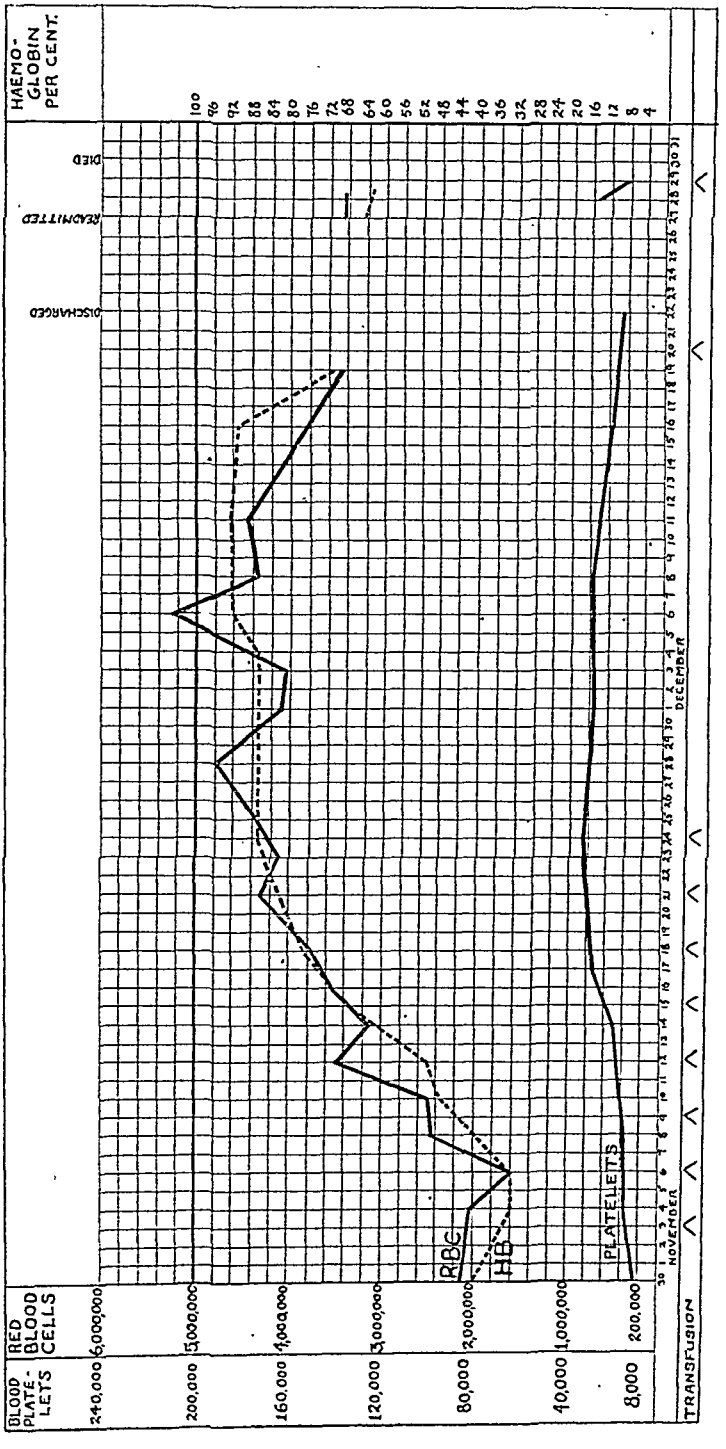

HAEMO-GLOBIN PER CENT.
RED BLOOD CELLS
BLOOD PLATE-LETS
DISCHARGED
READMITTED
DIED
RBC
HB
PLATELETS
TRANSFUSION
NOVEMBER
DECEMBER

CHART I

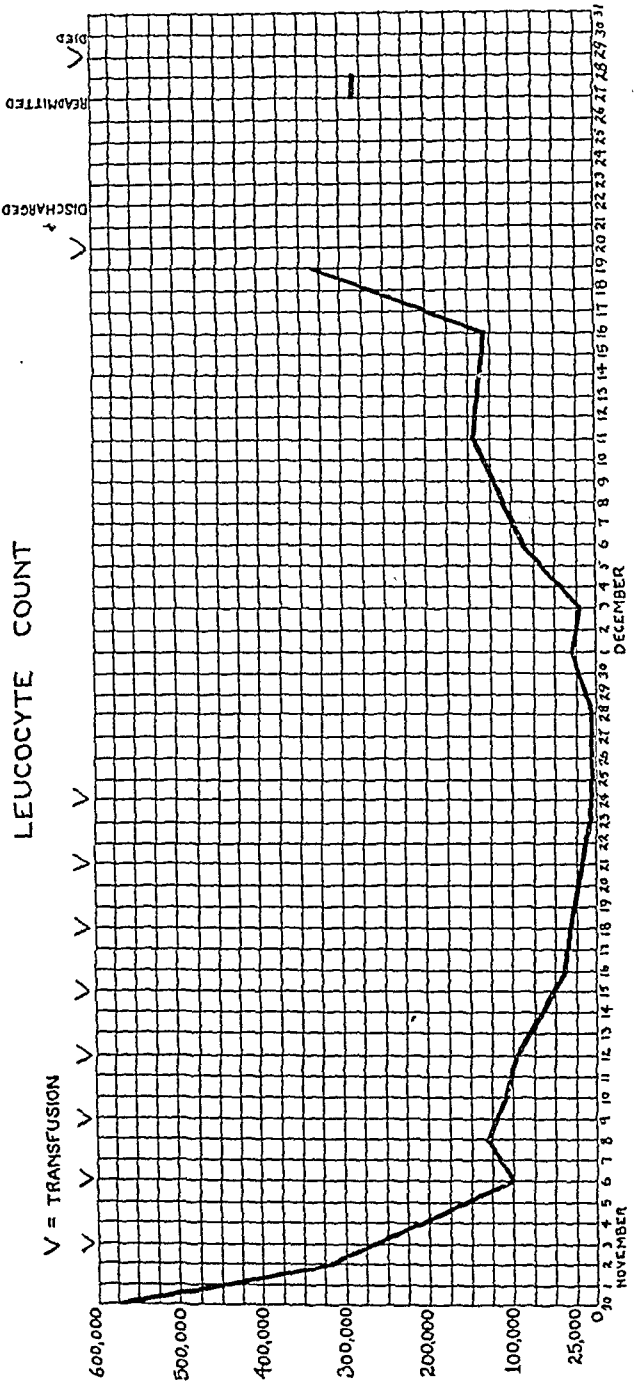


CHART II

and the diagnosis of leukemia had to be questioned, but the extremely high counts previously recorded seemed to force the maintenance of this diagnosis.

Active treatment was now lessened and transfusions stopped. No return of anemia was noted, but the total white count commenced little by little to rise. Within a week it rose from 4800 to 83,400 of which latter figure 79 per cent were lymphocytes. A week later

143,000 was reached; still without any drop in the red blood cells or hemoglobin. At this time petechiæ reappeared and the tourniquet test was found to be again positive.

On December 19 the patient was definitely less well; there were many petechiæ and the glandular enlargement was increasing. The white cells had risen to 333,400 and the red cell count and hemoglobin had begun to drop. New glandular enlargements made their appearance, especially a flat swelling in front of each ear suggesting a parotid swelling. The spleen was now very large. Hearing became less acute and the mental state approached coma.

A few days later oozing from the nose recommenced, and coma deepened. Finally death occurred in coma from cardiac failure.

Necropsy. At necropsy, the characteristic findings of lymphatic leukemia were found. All lymph nodes were enlarged and hemorrhagic; the spleen and liver were enormously enlarged and were infiltrated throughout with masses of lymphoid cells. There were hemorrhages scattered throughout various organs and on serous surfaces.

Discussion of Case. There are many reports in the literature of cases in which a diagnosis of acute leukemia had to be abandoned for one of infectious mononucleosis upon the cure of the condition (see Türk [19]).

In this case, however, the picture at first was so definitely that of acute leukemia that we were unwilling to change our diagnosis even when the total count fell to normal. The possibility of infectious mononucleosis was discussed at that time and this diagnosis ruled out because of the very high counts obtained at first. Remissions occur in almost every known blood disease, including chronic leukemia, pernicious anemia, and even in acute leukemia, and in the present instance we believe that the remission was perhaps initiated by the active treatment and the transfusions. What would have happened if it had been possible to continue the free use of transfusions we can only speculate.

Even if the total count had not been so great, we believe that a study of the lymphocytes would have strongly suggested that the case was one of leukemia rather than one with simply an increase of normal lymphocytes. Certainly the blood picture differed from what might be seen in a case with simple lymphocytosis, as for example whooping cough; but did approach more nearly the blood picture of infectious mononucleosis. It is quite possible to believe that, certainly on the blood picture alone, it would be impossible to differentiate between certain cases of infectious mononucleosis and acute leukemia; and on the other hand, if the cases of whooping cough with very high total counts and lymphocytosis be accepted, it must be admitted that such a blood would be differentiated from a chronic lymphatic leukemia with great difficulty.

Summary. It is important in hematological reports to define just what is meant by the terms employed. Confusion has resulted from a failure to do this. Only by careful reports can the proper distinction between true lymphocytosis, acute lymphatic leukemia and infectious mononucleosis be made.

The syndrome agranulocytic angina does not apparently deserve to be considered a special entity but merely one type of reaction to severe infection.

A case of acute leukemia is reported, of the lymphatic or lymphoblastic type, in which during a remission, perhaps induced by treatment, the blood picture passed through stages at which it closely resembled infectious mononucleosis and even reached the stage where it resembled the picture of agranulocytic angina. A rapid return of the leukemic blood picture, however, followed with fatal outcome.

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THE INFLUENCE OF REST, SLEEP AND WORK UPON THE ACTION OF THE HEART.

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If, according to the procedure of Huerthle,[1] systole be determined as the time from the beginning of the first to the beginning of the second heart sound, then the proportionate duration of the

systole, the "time of action," compared with the time of the entire heart period, amounts to an average of 33.5 per cent to 37.5 per cent in the healthy adult with a pulse rate of between 50 and 78 beats in a minute, as Brugsch and Blumenfeldt[2] have found. From that, as calculated for the period of twenty-four hours, a working time of approximately eight hours results for the human heart, provided, of course, that within that term equal work, neither too hard nor too easy, be performed by the heart muscle. In order to ascertain whether and to what extent this "eight-hour working day" of the normal heart is altered by physically exhausting labor or, on the other hand, by rest in bed of longer duration and by sleep, and in order to find out what effect rest and motion exercise upon the time of action and upon the time of electric stimulation of the ventricles, electrocardiographic and cardiophonographic examinations were made of the same individuals, first in the usual condition, then in the state of rest and sleep, and finally immediately after the performance of increased muscular activity.

The investigations were made of individuals: (1) With healthy hearts; (2) with valvular diseases; (3) with tachycardia; (4) with bradycardia, persons of various ages and both sexes being selected.

All researches, having been preceded by case history, auscultation, percussion, Roentgen ray examination, and determination of the blood pressure, were done with Einthoven's string galvanometer and with Frank's cardiophonograph which was attached to the apparatus, so that each film contained two electrocardiographic (Derivations I and II), one cardiophonographic, and one chronometric curves.

Normal Curves. Of each person three films were made, the first in an "indifferent" condition of the heart, that is, just as the patient had come into the room, without having rested or done any hard work. In the following, we shall speak of these curves as "normal curves" or "usual day curves."

Sleeping Curves. The object of the second photograph was to observe the influence of prolonged rest and of sleep upon the action of the heart. To obtain this, the writer had the persons examined lie on their backs for one hour and a half in the darkened room, with avoidance of speech and all other movements, the electrode cuffs and the phonographic heart drum being left on. After that time the majority of the persons were found to be asleep. With the exception of 1 case where bromids were given, the writer abstained from the production of artificial sleep for fear of an eventual falsification of the result by the influence of the drug employed upon pulse rate and time of action. Not always, it is true, could the continuous psychic excitement, though diminished by suggestive means, be eliminated, especially in neurasthenic and psychopathic individuals, an excitement that was also partially based on the rather unusual situation. Therefore, only such persons were used

who either had gone through an electrocardiographic examination before or who prior to their own examination had watched that of another person so that they could convince themselves of the harmlessness of the procedure. In one of the cases a deviation from the rule was noticed when the noise of the starting motor awakened the patient, when, instead of the sleeping curve, one immediately after awakening was taken.

Resting Curves. In all those cases where sleep could not be obtained, it was tried at least to produce a sleep-like rest during which the subjects, according to their own statements, "dozed" or "drowsed." We shall speak of such photographs as "resting curves" and reserve the term "sleeping curves" for those cases where the examiner was fully convinced that the pictures were taken during regular sleep.

Working Curves. The second film was followed by the working experiment. The exertion consisted in most cases in about 20 to 25 deep genuflections, and where for some reason they appeared unsuitable, in pushing the arms forward, sideward, and upward, or in the movements of carpet beating, so that a noticeable fatigue with increase in the pulse rate resulted. In patients with advanced decompensation of the heart such procedures were naturally contraindicated. Here a repeated sitting up and lying down in bed was prescribed in order to obtain the effect desired. The pictures taken about thirty seconds after the termination of the movements will be called "working curves."

Influence upon the Time of Action. As the most important result of the valuation of the influence of rest, sleep and work upon the heart in the examination of 25 persons, there was an almost invariable correspondence of the time of action with the pulse rate. The absolute duration of systole is inversely—the proportionate duration of the systole, directly—proportional to the number of heart beats; the faster pulse corresponds with a longer time of action. As is well known, the pulse rate becomes lower in the condition of complete bodily rest with absence of psychic excitement—the writer has observed differences up to 36 beats in a minute—on the other hand, it is increased to more than one and a half times by physical exertion and coarse psychic emotions such as fear, fright, anger or expectation. Hence, with the slackened action of the resting heart, that is with the prolongation of the single heart period, an increase in the absolute, a decrease in the proportionate duration of the systole naturally corresponds, while during work the accelerated heart action results in a reversal of these conditions.

The time of action is reduced in the condition of rest, prolonged during work.

In the adult with a healthy heart the time of action amounts to 31 per cent to 35 per cent during rest and to 34.5 per cent to 39.5 per cent under the influence of work. Hence, deviations from the

normal average of 33.5 per cent to 37.5 per cent are present, but in the healthy adult not very considerable. The difference is for rest about — 2 per cent, for work up to + 7 per cent.

There exists, as is seen, a constant proportion between pulse rate and time of action, in that the influence of rest and work upon the proportionate duration of the systole can be valued upon the reduction or the increase of the pulse rate.

This is true not only for the healthy, but invariably for each heart. No matter whether we have to deal with a normal pulse rate, or the action of the heart be accelerated as is found in children and decompensated states, or whether we are dealing with the bradycardia of a vagotonic, in every case the time of action appears reduced corresponding with the lower pulse rate, and is prolonged during work.

Special mention should be made of the fact that where there is a fluctuation in the duration of the entire heart cycle, either in the harmless respiratory arrhythmia or in the pulsus irregularis perpetuus, the absolute duration of the systole is always just about the same and does not follow the fluctuation to which, therefore, only the diastole is subject. In such cases it is necessary to calculate the proportionate duration of the systole, the real time of action, from the average of as great a number of heart beats as possible.

A few examples may serve for illustration of the conditions described.

TABLE I.—PULSE RATE AND TIME OF ACTION.

Name.	Age.	Condition.	Curve.	Pulse rate.	Time of action, per cent.
L. K.	26	Healthy	Normal	68	32.13
			Sleeping	58	31.65
			Working	96	39.55
F. B.	34	Healthy	Normal	89	43.18
			Resting	75	40.82
			Working	102	49.22
H. T.	35	Mitral and aortic insufficiency	Normal	92	49.04
			Sleeping	86	47.06
			Working	99	48.42
W. T.	55	Arrhythmia perpetua	Normal	98	39.50
			Sleeping	74	32.99
			Working	110	43.66

It must be mentioned that, as regards time of action, there are no differences between the sleepless rest which is free from psychic excitement, and the real sleep. The only standard factor is, in both conditions, the number of pulse beats. Uneasy sleep with increased pulse rate, accordingly, exhibits an increased proportionate duration of the systole. A sixteen-year-old boy, who in the usual day curve in connection with 83 pulse beats had a time of action of 40.72 per cent, showed in the sleeping curve because of a tormenting, exciting dream a frequency of 104 beats and a time of action of 49.71 per cent! As such occurrences are comparatively

rare, we may say that during sleep both pulse rate and time of action are reduced.

If the time of action in the normal condition and that during rest be calculated on the basis of twenty-four hours and the results be compared with one another, then we find for the rest in two of the examined cases a shortening of only fifteen minutes; this reduction amounts in general to about thirty to forty-five minutes and has its maximum in a work saving of one and a half to two hours. Given a night's rest of eight hours and not too hard work during the day, the time of action of a healthy adult heart with a proportionate duration of the systole of about 33.5 per cent on the normal curve would be not eight hours, but about seven and seventy-five-hundredth hours. It must, however, be borne in mind that the resting and sleeping curves were already all taken after one hour and a half; in a continuously recumbent position of seven to eight hours' duration during the night or in rest in bed of several days the pulse rate and, accordingly, also the time of action often undergoes a more considerable diminution, so that then the heart may rest daily about one and a half to two hours longer than it usually does.

Influence upon the Pulse Rate. Our opinion coincides with the results of Klewitz's[3] researches on the pulse rate during sleep, according to which the reduction in the pulse rate is greater during the night's sleep than during the day's sleep. The difference is, of course, very low: On the average about 1.6 beats per minute. According to Klewitz, the average pulse reduction during the night is 14.8 beats; for the day's sleep the writer has found a reduction of 13.2 beats, as the following table demonstrates:

TABLE II.—INFLUENCE OF SLEEP ON PULSE RATE.

Age.	Diagnosis.	Normal pulse.	Pulse during sleep.	Difference.
24	Bradycardia	50	48	2
26	Healthy	68	58	10
25	Drop heart	68	62	6
34	Healthy	89	75	14
12	Tachycardia	128	92	36
35	Mitral insufficiency	92	86	6
41	Hysteria	99	71	28
23	Mitral insufficiency	71	69	2
37	Mitral stenosis	84	75	9
24	Tachycardia	141	133	8
55	Arrhythmia perpetua	98	74	24
	Average			13.2

As we see, the maximum value for the reduction of the pulse rate by rest in day time is 36, the minimum value is 2 beats per minute. That restless sleep may cause an increase of the pulse rate, has been mentioned above.

As Klewitz already demonstrated, there are, referring to this,

no differences between healthy and decompensated hearts, while in a case of decompensation in a man, aged seventy-six years, with a totally allodromic electrocardiogram and a frequency of 144 beats rest which, it is true, was interrupted by coughing spells, did not result in a reduction of the pulse.

The increase in the pulse rate after work may also be illustrated by a series of examples.

TABLE III.—INFLUENCE OF WORK ON PULSE RATE.

Age.	Diagnosis.	Normal rate.	Rate during work.	Difference.
26	Healthy	68	96	28
25	Drop heart	68	73	5
34	Healthy	89	102	13
35	Mitral insufficiency	92	99	7
15	Healthy	74	79	5
48	Mitral insufficiency	69	80	11
31	Neuralgia	75	82	7
20	Healthy	56	64	8
23	Mitral insufficiency	71	81	10
52	Mitral insufficiency	56	62	6
37	Mitral stenosis	84	88	4
55	Arrhythmia perpetua	72	84	12
57	Arteriosclerosis	98	110	12
Average				9.8

Hence, work causes an increase of about 10 beats per minute in the pulse rate. Under work is understood the exertion described above, and it is natural that continuous labor yields higher values than those given here.

Influence upon the Time of Electric Stimulation. In addition to the finding that rest and sleep cause a reduction, work an increase of pulse rate and time of action, we observed as a second important result of the investigations a regular alteration of the relation between the time of action on the one hand and the proportionate time of electric stimulation on the other hand. Brugsch and Blumenfeldt[4] were the first to elaborate in a systematic way the comparison between ventricular electrogram and ventricular phonogram, a comparison which has also been studied by the writer in normal and pathological films.

The result of the comparison was that *during work the ventricular electrogram is always longer, and during rest and sleep always shorter than the ventricular phonogram.*

In the healthy adult where the difference between the two is equal to, or almost equal to zero, it becomes negative during rest and positive during work. If the difference is *a priori* quite high in favor of the electrogram, as is the case in younger years or in pathologic heart conditions, it sinks—remaining positive—considerably during rest and climbs during work.

TABLE IV.—EFFECT OF REST AND SLEEP ON RELATION OF VENTRICULAR ELECTROGRAM TO PHONOGRAM.

Age.	Diagnosis.	Normal relation, per cent.	Relation during rest, per cent.	Difference, per cent.
34	Healthy	0	−2.100	2.100
20	Healthy	0	−0.920	0.920
23	Mitral insufficiency	0	−1.440	1.440
41	Hysteria	0.140	−0.890	1.030
24	Bradycardia	0.430	−0.950	1.380
16	Lymphatism	0.660	−0.287	0.947
12	Tachycardia	0.885	−1.047	1.932
48	Mitral insufficiency	1.320	0	1.320
26	Healthy	1.356	−1.670	3.026
25	Drop heart	1.827	−2.470	4.297
15	Healthy	4.710	0	4.710
31	Neuralgia	5.230	1.610	3.620
52	Mitral insufficiency	6.640	5.990	0.650
55	Arrhythmia perpetua	6.830	5.150	1.680
57	Arteriosclerosis	7.750	2.300	5.450
37	Mitral stenosis	10.680	4.950	5.730
14	Tachycardia	16.120	8.020	8.100
76	Hypostatic pneumonia	14.500	9.000	5.500
	Average			3.000

The minus sign − indicates the shorter duration of the electrogram.

TABLE V.—EFFECT OF WORK ON RELATION OF VENTRICULAR ELECTROGRAM TO PHONOGRAM.

Age.	Diagnosis.	Normal relation, per cent.	Relation during work, per cent.	Difference, per cent.
34	Healthy	0	1.77	1.770
20	Healthy	0	1.03	1.030
20	Mitral insufficiency	0	0.56	0.560
41	Hysteria	0.140	1.17	1.030
24	Bradycardia	0.430	1.26	0.830
16	Lymphatism	0.660	0.75	0.090
12	Tachycardia	0.885	1.99	1.105
48	Mitral insufficiency	1.320	3.46	2.140
26	Healthy	1.356	5.77	4.414
25	Drop heart	1.827	1.88	0.053
55	Arrhythmia perpetua	6.830	9.78	2.950
52	Mitral insufficiency	6.640	6.76	0.120
76	Hypostatic pneumonia	14.500	22.00	7.500
	Average			1.800

From the two last tables it appears that the shortening of the electrogram when compared with the phonogram, amounts to an average of 3 per cent up to a maximum of 8 per cent, its prolongation after work to an average of 1.8 per cent up to a maximal 7.5 per cent. In other words, a dissociation is being produced between the duration of the mechanical action and the time of the electric stimulation of the ventricles under the influence of work in favor of the ventricular electrogram, but under the influence of rest, at its cost.

It is striking that the nature and height of said dissociation does not seem to have any direct relation to the pulse rate. In the above mentioned case of the man, aged seventy-six years, with a totally decompensated heart where the pulse in the normal, the resting and the working curves remained invariably at the same rate of 144 beats, there were, nevertheless, considerable differences in the time relation between ventricular electrogram and phonogram, namely, a shortening of 5.5 per cent at rest, a prolongation of 7.5 per cent at work, that is, an interval of full 13 per cent between rest and work. In a woman, aged thirty-one years, who, in the resting curve on account of intercurrent psychic emotions, had an increase of the pulse rate of 2 beats per minute compared with the normal curve, the ventricular electrogram was shortened at a rate of 3.62 per cent. In another case where, under the influence of a vagus stimulation immediately after work, the pulse rate had dropped from 50 to 45 beats, there was still a prolongation of the electrogram of 0.83 per cent, compared with the normal condition. Many more such examples could be cited. They all show that the regularity in the described relation between the time of electric stimulation and the time of mechanical action is not at all changed, even by alterations in the pulse rate.

It must further be noted that the stated prolongation of the time of electric stimulation after work outlasts the existing increase in the pulse rate for two to three minutes and, therefore, can still be elicited when the faster pulse has already slackened to the normal or has even reached a frequency lower than normal.

Thus, in each case, work causes a prolongation, rest and sleep a reduction of the time of electric stimulation of the ventricles, as compared with the time of mechanical action.

Influence upon the Time of Conduction. Another subject of the experiments was the time of conduction, that is the interval from the end of the auricular P wave to the beginning of the Q wave, during rest and work. The following table gives the results.

TABLE VI.—P-Q INTERVALS (TIME IN TWENTY-FOURTHS OF SECONDS).

P–Q normally.	P–Q during rest.	P–Q after work.
2.9	3.1	2.0
2.9	3.2	2.2
1.7	2.0	1.5
1.8	2.0	1.5
3.2	3.4	3.0
2.0	2.4	1.5
1.2	2.0	1.5

The table shows that the duration of the conduction of the electric stimulation through the bundle of His is absolutely prolonged during rest and absolutely shortened during and immediately after work. A great number of calculations have demonstrated that there is no

constant ratio governing the percentage relationship between the time of conduction on the one hand and the entire heart period or the duration of the diastole on the other hand. It was also interesting to find that in 1 case of pulsus irregularis perpetuus and auricular fibrillation with about 150 contractions of the auricles in a minute there was no change in the frequency of the auricular contractions though the original pulse rate of 98 went down to 74 during rest and up to 110 during work.

Influence upon Arrhythmias. The few cases of arrhythmias which were examined, demonstrated sufficiently that the irregularity as such always persists, but that in the condition of rest and sleep the difference between the single, prolonged heart periods becomes greater, while under the influence of work they appear to be about the same as on the usual day curve.

One illustrative example follows:

W. T., aged fifty-five years; pulsus irregularis perpetuus.

TABLE VII.—DURATION OF HEART PERIODS GIVEN IN ONE-TWENTY-FOURTHS SECONDS.

	Usual condition.	Sleep.	Work.
	10.0	12.6	20.2
	15.0	30.2	13.2
	13.0	16.5	13.4
	13.6	10.1	8.6
	11.4	22.6	16.4
	16.2	19.0	8.2
	17.6	14.9	10.6
	9.2	21.4	15.5
	16.0	11.0	8.3
	16.5	36.0	16.2
Greatest difference	8.4/24	25.9/24	12.0/24

While under usual conditions and after work the longest difference in time between 2 of 10 heart beats on the table amounts to about half a second, it goes up during sleep to about twice as long a time, that is, to one second; this means that on the same resting or sleeping film of such a case one heart period may last one full second longer than another heart period.

We may mention here, too, that in 1 case, that of a woman, aged fifty-two years, whose extrasystoles had completely disappeared after prolonged medication with digitalis, the extrasystoles came back during the working experiment while they had not been present in the resting or in the usual curve.

Influence upon the Form of the Electrocardiogram. In order to study the influence of rest and work upon the form of the electrocardiographic waves, the writer had to eliminate the effect produced by the variations of the tension of the strings in that immediately before each of the three films (normal, resting, working) he gauged

the apparatus anew and kept the strings always at the same tension of 40 mm. Under such precautions, no difference, neither in the form nor in the amplitude of the single waves, could be found. The ventricular quotient $R-T$ had in each case a constant value for each of the three films.

Conclusions. 1. With the increased pulse rate after work there is a corresponding increased time of action; with the diminished pulse rate in the condition of waking rest and during sleep there is a corresponding diminished time of action.

2. Regarding time of action and time of electric stimulation, there is no difference between sleepless rest and sleep. Uneasy sleep with exciting dreams results in an increased pulse rate with prolonged time of action.

3. There is an alteration in the relation between the time of mechanical action and the time of electric stimulation under the influence of rest, sleep and work. During rest, the ventricular electrogram is shorter, after work longer than the ventricular phonogram. This prolongation of the ventricular electrogram after work outlasts the increase in the pulse rate for two to three minutes.

4. The time of conduction of the electric stimulation through the bundle of His is absolutely prolonged during rest, absolutely shortened after work. There is no law in its proportionate relation to the duration of the entire heart period or to the diastole.

5. In arrhythmias the difference in time between the single heart periods is increased during rest, diminished under the influence of work.

6. Extrasystoles which had disappeared after digitalis medication, reappeared during work.

7. Form and amplitude of the electrocardiographic waves remained unaltered.

8. Age, sex and blood pressure had no influence upon the conditions described.

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THE POSITIVE CENTRIFUGAL VENOUS PULSE.

With a New Method for its Detection.

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Tricuspid insufficiency of organic origin occurs very infrequently, but relative insufficiency of this valve is an almost inevitable consequence of cardiac decompensation of whatever source at some stage in its progression. Minor degrees of regurgitation doubtless occur under varying changes in the circulatory load as a result of the disadvantageous construction and support of the tricuspid valve; but it must be appreciated that any temporary advantage accruing to the right ventricle through this occurrence, is gained at the expense of the feeble right auricle and cannot be long sustained. This safety mechanism[1] to protect the right ventricle from overdistention has then distinct limitations. In this relation it is important to consider the position of the right ventricle in compensation. For all pulmonic lesions the load of circulatory imbalance is first met by the right ventricle. In all mitral lesions and in aortic lesions attended by relative mitral insufficiency the increased pressure in the pulmonic circuit is ultimately compensated for by primary hypertrophy of the right ventricle; and the final step in decompensation in left-sided heart lesions is dilatation of the right ventricle, leading to relative tricuspid insufficiency by one of two mechanisms. In some instances dilatation of the right ventricular wall operating through the papillary muscles and attached chordæ tendineæ on the free margins of the tricuspid valve eventually induces relative inadequacy in failing compensation. Or, depression of tone of the sphincter-like muscle fibers supporting the tricuspid ring may explain another group of relative insufficiencies.

The recognition of tricuspid regurgitation would, therefore, seem most important from a prognostic standpoint. The direct examination of the heart may reveal enlargement to the right. The complicating nature of relative tricuspid insufficiency explains the confusion of murmurs which commonly attends auscultation in these cases. Then, too, the weakened myocardium and the dilated tricuspid orifice are further mechanical reasons for lack of definition and absence of murmurs. Typically the murmur of tricuspid insufficiency is a soft, blowing systolic one, best heard at the xiphosternal junction to the left and transmitted up and to the right. Were the diagnosis of tricuspid insufficiency to rest on the examination of the heart alone, the majority of cases would pass unrecognized.

Since the influence of tricuspid regurgitation is reflected through distention of the right auricle back on the systemic venous return, venous engorgement, anasarca, albuminuria with reduced urinary output and more or less profound changes in the higher nervous functions dependent on disturbed circulation may be anticipated. As direct manifestations of these changes in the venous circulation, the positive centrifugal venous pulse in the jugulars and the pulsating liver have been held as practically diagnostic of tricuspid regurgitation by certain authorities.[2, 3]

Critical analyses of the venous pulse by graphic methods have failed to satisfy observers of the infallibility of its presence and significance. It is beyond the scope of the present consideration to discuss the interpretation of the phlebogram. Suffice it to state that Mackenzie[4] by clinical observations and Rihl[5] experimentally have established the fact that tricuspid regurgitation may occur without a positive venous pulse. Furthermore the ventricular form of venous pulse of Riegel[6] has been found to occur under other conditions than tricuspid insufficiency. Hewlett[7] gives three causes for the ventricular type of venous pulse, namely, simultaneous contraction of the auricles and the ventricles (as in heart block and extrasystoles), paralysis of the auricles and tricuspid insufficiency. Mackenzie[8] writes: "They have, therefore, regarded the ventricular form of the venous pulse as only a sign of tricuspid regurgitation, and have missed the real significance of this very important symptom. That it is a sign of tricuspid regurgitation there is no doubt, but it is a sign of far greater significance, namely, that the auricle does not precede the ventricle in the cardiac cycle." Vaquez[9] states that "contrary to the opinion of the older authors, examination of the venous circulation gives no indication whatever of the presence or absence of tricuspid insufficiency. It is to the disordered functioning of the auricle and not to the reflux of blood that we must attribute the phenomena of venous pulse and the ventricular form of the tracings."

Venous tracings are difficult to obtain and to interpret at times. Furthermore, much doubt has been cast on the pathognomonic significance of the ventricular form of venous pulse in tricuspid regurgitation by the above stated data. On the other hand study of the veins of the neck by direct inspection is frequently unsatisfactory by reason of the overactivity of the carotids. Furthermore, Vaquez[9] dismisses the importance of visible jugular pulse thus: "The sign that they thought almost pathognomonic was the systolic filling of the jugular vein after it had been emptied by pressure of the finger. Now, this sign which Potain also rejected, is of no value because it may be absent in undoubted tricuspid insufficiency and may exist in the absence of that lesion. It results not from the reflux of the blood through the tricuspid orifice, as was wrongly believed, but from the retrograde shock communicated by the

ventricular contraction to the column of blood retained in the auricle and in the jugular veins. The phenomenon of the venous pulse indicates that there is a stasis of blood in the auricle without prejudging the cause."

In cases of unquestionable tricuspid insufficiency, however, Osler and McCrae[3] report the presence of the regurgitant pulse wave not only in the jugular veins but also "in the subclavian and axillary veins and even in the subcutaneous veins over the shoulder, or in the superficial mammary veins." Mackenzie,[4] in addition to remarking like propagation of venous pulse waves, noted their presence in the small veins of the arm (twice) and in the veins of the face (once). He suggests the facilitation of these observations by the application of a thread of sealing wax to the skin overlying the vein, as suggested by King, or the sprinkling of pulverized glass mirror over the vein, after Czermak and Hippesley.

In the course of routine venous pressure studies of an individual seriously decompensated and showing a high venous pressure, a pulsation synchronous with the radial arterial pulse and centrifugal in direction was remarked in the superficial veins of the forearm and the dorsum of the hand. This venous pulse was exaggerated in expiration. This interesting observation led to a close scrutiny of the peripheral veins in all cases of cardiac decompensation and in certain types of compensated cardiac disease, as well as in a large control group.

The results which will be summarized shortly, were quite striking; and in the course of these studies an interesting and an apparently new factor in eliciting the centrifugal venous pulse was noted. The following case of cardiac decompensation with relative tricuspid insufficiency is quoted as presenting characteristic findings:

Case Report. W. B., aged sixty-nine years, presenting the classical picture of hypertension—myocarditis, is admitted in the third attack of cardiac decompensation. Dyspnea, swelling of the ankles and abdominal distention are his subjective complaints. Orthopnea, anasarca and cyanosis are established. A positive, centrifugal jugular pulse is suggested. Great numbers of coarse, moist rales are heard in both bases. A wavelike cardiac impulse is detected in the fourth and fifth left interspaces, anterior axillary line. No thrill is felt. The right and left cardiac borders in the second interspace are 38 and 30 mm.; in the third, 38 and 92 mm.; in the fourth, 51 and 150 mm.; in the fifth, 160 mm. (well into left axilla). The apical first sound is replaced by a loud blowing systolic murmur which is transmitted well to the axilla and the back. The pulmonic second is markedly accentuated. Softening of the aortic first sound with accentuation of the second is determined. The rhythm is regular. The vessels are tortuous and beaded. Blood pressure registers systolic 172 mm., diastolic 116 mm. The liver

extends 10 cm. below the costal margin in the right midclavicular line, but no expansile pulsation can be determined. Casts and albumin are present in the urine.

The venous pressure is 24 to 26 cm. of water. When the hand is elevated to a level 26.5 cm. above the midaxillary line (patient recumbent), a positive centrifugal pulse appears in the veins on the dorsum of the hand. Careful observation reveals no venous pulsation with the hand at a lower level and a sharp recurrence at the point of collapse of the vein. In the course of partial reëstablishment of compensation this phenomenon persisted without exception on daily examinations, until the venous pressure fell below 12 cm. fifteen days later. Its infallible appearance under the conditions stated was established many times.

In this case arterial hypertension and cardiac hypertrophy were apparent; and in addition there were unmistakable evidences of relative mitral insufficiency. Tricuspid insufficiency may be inferred from the jugular pulse, anasarca and hepatic congestion. The high venous pressure was suggestive of a damming back from the right heart. The appearance of a centrifugal venous pulse when the arm or hand was elevated to a level above the right auricle equivalent to the venous pressure, constituted a new observation in our experience.

In all, 14 cases showing clinical evidences of cardiac decompensation of such degree as to indicate probable right heart failure (comparable with (the case reported) have been studied with this point in view. Of this group 10 cases showed the centrifugal pulsation in the peripheral superficial veins of the forearm and hand, only when these parts under observation were elevated above the right auricle a distance equalling the venous pressure, or just before collapse of the vein was effected. At times it was difficult to judge whether the pulsation was more apparent at a point immediately below or just above that at which the veins collapsed; but as a rule the change was sharp and clear cut. In the remaining 4 cases centrifugal pulsation was noted in the superficial veins with the forearm on a level with the right auricle; but even in these cases the pulsation became perceptibly greater and clearer as the arm was elevated a distance equivalent to the venous pressure. Three of the 14 cases showing inferential evidence of tricuspid insufficiency and the positive centrifugal venous pulse have come to necropsy. In all of these cases, right-sided cardiac dilatation was marked. The measurements of the tricuspid valve were 12, 12 and 13.5 cm., respectively. The last figure alone is above the normal maximal figure; but the first two represent the upper limit of normal and for the female (as represented by the subjects) are possibly somewhat excessive. In any event stretching of the valve ring is not essential to a relative insufficiency and these cases unquestionably represent examples of

the mural myocardial stretch operating through the papillary muscles and the chordæ tendineæ to induce tricuspid insufficiency. In the surviving cases, a disappearance of the centrifugal venous pulse attended the reëstablishment of adequate compensation and the subsidence of signs of tricuspid incompetency. As a rule this point coincided with a venous pressure fall to 10 to 12 cm. but occasionally the venous pulse persisted with the venous pressure as low as 7 cm.

Control cases were studied to establish the possible appearance of this phenomenon in conditions other than those suggestive of tricuspid regurgitation. In no normal individual has it been observed, nor has it been seen in well-compensated cardiac lesions. No simple extrasystolic arrhythmia has shown the positive centrifugal venous pulse. Only 1 case of heart block has been available for study, and here again no such pulsation was remarked. In none of the 8 cases of fairly well compensated auricular fibrillation studied has this venous pulsation been noted. It has not been observed in any of 5 cases of pernicious anemia.

Elevation of the hand and forearm above the level of the heart apparently induces the simple hydraulic result of removing the inertia of a long column of blood in the veins of the arm, so that the relatively low pressure of blood thrown back into the auricle and the venous trunks by the right ventricle through the incompetent tricuspid valve may effect perceptible pulse waves. The small group of cases in which the regurgitant force was sufficient to produce the centrifugal pulse in the peripheral veins with the arm at the cardiac level and the improved visibility of even these waves on elevation of the part constitute evidences for the truth of the above explanation. In practice the radial vein is chosen for observation. A segment of this vessel is studied in an oblique light, the observer supporting the forearm and varying its level above and below the point of collapse of the vein. As a working basis the midaxillary line in the recumbent posture and the xiphosternal junction in the sitting or erect may be taken as the level of the right auricle. Visibility is improved by painting a small area of the skin overlying the vein with common aluminum paint. The direction of the wave is readily established by pressure on the vein above or below the point of study. Pressure proximal will obliterate the centrifugal venous pulse; distal, increases the same.

Conclusion. It is suggested that a simple procedure of elevating the arm may establish the presence of a positive centrifugal venous pulse in the radial vein in cases of relative tricuspid insufficiency and that this phenomenon is not observed in normal controls or in any of the conditions under which the ventricular type of venous pulse has been described, other than tricuspid insufficiency.

NOTE: Since submitting the proofs of this article, an admirable and exhaustive paper on the "Peripheral Pulsation in the Veins in Congestive Failure of the Heart" by William J. Kerr and S. L. Warren has appeared in the *Archives of Internal Medicine*, 1925, 36, 593.

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RAYNAUD'S DISEASE.[1]

LIMITATIONS OF THE CLASSICAL PICTURE AS A GUIDE TO DIAGNOSIS; REPORT OF A CASE SHOWING EXTENSIVE BONE INVOLVEMENT.

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Much has been written since the days of Raynaud about the group of phenomena which now bears his name. In spite of this, however, how much have we actually added to our knowledge of this condition? Very little. Like Raynaud, we are compelled to reason to a vasomotor disturbance as the immediate cause of the gangrene, but as to the cause of this vasomotor disturbance, or its cure, we know as little as did Raynaud himself. One encouraging fact is to be noted, however. As more and more investigators have reported their observations, the term "Raynaud's disease" has come to include a wider and wider clinical picture. Under this heading we now find record of cases that have not advanced to a truly gangrenous stage, of gangrenes involving the deep as well as superficial structures, and of all manifestations of interference with the vasomotor mechanism in general, whether or not these were included in the original picture by Raynaud.

This modern tendency to extend the term Raynaud's disease beyond the classical picture has been noted by more than one medical writer, with approval by some, with disapproval by others. The suggestion has more than once been made that the term Raynaud's disease should be confined to the condition as described

[1] Read before the Faculty Clinical Meeting, St. Elizabeth's Hospital, Chicago, January, 1925.

by Raynaud, and that if one wishes to extend the picture another name had better be suggested.[2]

Regarding this we can only say that one's opinion thereon must be determined in a large measure by his opinion on the extension of eponyms in general. The question is an open one. To the writer it seems that this modern habit of ticketing with different names various phenomena which time and investigation have shown to be but different manifestations of the same affection is one of the great stumbling-blocks in the medical profession. Better the wider application of a name already established (even though it be an eponym) than the introduction of a new term which places the subject under a new heading in the various medical indexes. It is, therefore, with a two-fold purpose that the present paper is undertaken; first, to urge the further extension of the term Raynaud's disease to include all gangrenes, moist or dry, symmetrical or asymmetrical, deep or superficial, which give evidence of being due to defective vasomotor influence (as Raynaud himself undoubtedly meant it to include); second, to record a case of Raynaud's disease which the writer believes to be unique in both its symptomatology and its postoperative findings, and which was instrumental in calling to the writer's attention the fact that Raynaud's disease is not always attended by the classic Raynaud phenomena.

With Raynaud's original thesis on "Local Asphyxia and Symmetrical Gangrene of the Extremities" (1862) most readers are familiar. It was his purpose "to demonstrate that there is a kind of dry gangrene affecting the extremities which it is impossible to explain by vascular obliteration," and he hoped to prove that "this kind of gangrene has its cause in a vice of innervation of the capillary vessels." Regarding symptoms, he says, "The commencement takes place in different ways. In one case the extremities become pale, exsanguine, and then take on a lilac tint; tinglings or shooting pains occur—accompanied by numbness, but are soon replaced by burning heat; changes of color take place, violet becomes more pronounced—Area icy cold. Sometimes a livid redness first appears—Livid marblings show themselves in the neighborhood of the affected parts, and rise to a great height over the corresponding limbs. The digits may become entirely black, small phlyctenulæ may appear first on one digit then another, which break and leave the derma naked; all the nails may fall. Sloughs are formed. Parchment-like appearance may supervene without the blisters. Skin takes on a drab color, dries up, and a conical form of the finger ensues. Desquamation follows and thickened particles of wooden hardness are raised up in shreds." Much more might be quoted

[2] A principle concurred in by the Editor: In the present instances, however, the inclusion of cases that fall within his basic thought of gangrene due to defective vasomotor mechanism seems proper, at least for such variations as Raynaud himself includes and without resorting to a *reductio ad absurdum*.

along the same line, but this is sufficient to show the wide variation of symptoms as observed by Raynaud.

It is the chief criticism of those who deplore the freedom with which obscure gangrenes are diagnosed as Raynaud's disease that modern investigators are introducing new features into the picture and obscuring some of the old ones. But what are the features of the classic picture of this disease—that is, the *essential* features—which modern investigators have obscured? What are the essential features of Raynaud's disease, anyway? Are they to be identified with a host of "symptoms" which even Raynaud, with his limited sources of data, found so variable? No one symptom or phenomenon of a disease can be considered an essential feature of a disease unless it be a constant factor, and no one of the phenomena described by Raynaud has shown itself to be a constant factor in all cases of Raynaud's disease—a fact which should amply justify modern medicine in extending the clinical picture until some constant factor shall finally be found.

The objection might here be raised that blackness and dryness were both constant factors in the cases reported by Raynaud—that it was "dry gangrene" which he especially set out to explain. This is partially true, for Raynaud designated the gangrene under his observation "dry." That the cases themselves did not always conform to this description, however, is indicated by his mention of those having "small phlyctenulæ, which fill with seropurulent liquid." The same is true of color, which Raynaud described in a general way as "black." In the cases recorded the blackness shows great variation, ranging all the way from "a marked violet color which finally disappeared to "a color as black as that produced by burns of the sixth degree." To me it appears that both these features of the disease as described by Raynaud were more accidental than essential and that, having so little else to guide him in selecting cases for study, he naturally hit upon those which showed these spectacular features. Raynaud was also inclined to regard symmetry as a very distinctive feature of the disease of which he wrote, yet this has been for some time recognized to be of only secondary importance. For the truly essential feature, or features, of Raynaud's disease, then—for the constant factors which shall finally point us on to the basic cause—we cannot look to the classic picture described by Raynaud, much as we may respect his scientific efforts.

Indeed, on going thoroughly into the recorded histories of this type of cases, one begins to wonder whether there is a single feature of Raynaud's disease, either as described by himself or later writers, that is not open to controversy as to its essentiality. A certain condition which one observer finds to obtain in the special case or cases under his observation may be totally lacking in the case of his fellow-worker. The conclusions at which one investigator

arrives may be wholly at variance with the conclusions of other equally careful and reliable investigators.

It needs but a brief survey of the literature on Raynaud's disease to demonstrate this. One writer reports his case of symmetrical gangrene as first manifested by a condition of local syncope or asphyxia, as did Raynaud. Another finds that instead of becoming cold and white, or blue, the case under his observation first became a fiery red. Again, the patient may show alternating syncope and asphyxia, as in the case herein reported, or even alternating asphyxia and active hyperemia, as in the case reported by Dr. Weber.

The mode of onset of the disease Raynaud described as sudden, lasting from only a few days to not more than a month, and the duration short. Osler also described the disease as beginning very suddenly and running an acute course to a rapid termination. Numerous others have found this item inconstant, the inception of the disease varying from an acute onset coming on almost instantaneously, as in the case reported by Hutchinson, to as long as four years, as reported by Hollis. A. H. Ferguson found that the disease was usually preceded by chronic symptoms. Its duration has varied from only a few weeks to several years. In some cases the disease has recurred year after year for an indeterminate period. In the case reported in this paper the onset of the disease was gradual, extending over a period of nine months before becoming acute, and the disease of long duration, covering a period of four years before amputation was finally submitted to. In the 67 cases reviewed by Buchanan the onset of the disease was "usually sudden, but sometimes gradual," and this elasticity of description becomes more and more necessary the more cases we consider.

The type of gangrene is not the same in all cases observed. "Dry gangrene," said Raynaud, and "dry gangrene" have echoed most of the recorders of these cases. But is dryness a necessary feature of Raynaud's disease? Absolutely, no! What law of anatomy or physiology can be invoked to establish the assumption that a gangrene due to vasomotor disturbance must of necessity be dry? I know of no type of vasomotor interference capable of producing dry gangrene that is not equally capable of producing moist gangrene under slightly varying conditions. Dry gangrene is the result of an interference with the efferent supply of blood, in which the anatomical area thus shut off will mummify if kept clean, and eventually be amputated by Nature at the terminals of the collateral vessels. Moist gangrene is produced when the efferent supply of blood is intact and the afferent blocked. These two types of circulatory interference give widely different clinical manifestations, but either may be due to a defective vasomotor mechanism. Raynaud's disease is, therefore, probably as often moist as dry, although the moist type has to date received little attention in medical literature. A limited number of cases have

been reported, however, such as that of Ferguson in which the gangrene was moist, and of Landry whose case showed "gangrene of both big toes, the right moist, the left more or less dry."

Regarding the areas involved, there is less difference of opinion among recent writers than between the earlier investigators and later ones. Raynaud considered the type of gangrene of which he wrote essentially a gangrene of superficial structures. Although he records cases where the phalanges were sloughed off at the joints he found no case in which the bone itself was involved. Osler describes the area subject to this disease as "limited to the terminal phalanges only." More recent writers report cases where the gangrene has involved much more extensive areas including the nose, ears, lips, gums, both hands, both feet, and even whole limbs. Deep structures as well as superficial have been affected, and bones have become atrophic, and even completely absorbed, without sloughing of the superficial tissues. In the writer's case almost the entire bony skeleton of the medial-anterior portion of the foot was destroyed, some of it being apparently absorbed, and some of it carried away in microscopic particles in a discharge which was found upon examination to be sterile. The external tissues finally became withered and dark, but, except for several blackened ulcers on the under and inner surfaces of the foot, the sloughing was done by the deep rather than the superficial structures.

The same wide difference of opinion is found to exist among medical men as to the predisposing and direct causes of this disease. To Raynaud a predisposing cause for this gangrenous condition seemed a logical necessity, and he attempted to find this cause in the age, sex and temperament of the individual affected. He considered heredity an important factor, and sexual excitation a very possible cause. On these points later investigators sharply disagree. Monro found that 8 per cent of the 180 cases he reviewed showed hereditary influence. "Family predispositions are not uncommon," says Osler. "Heredity plays no part," says Buchanan, which is the opinion of the majority of later writers.

So also with nationality. For many years it was considered that Raynaud's disease was especially a disease of the French and Hebrews—an opinion which is still held to some extent today, although the preponderance of opinion is now in the negative. "Raynaud's disease appears to be more common in England and France than in Germany. It is relatively more frequent among the Hebrews," writes Osler. In explanation of this he suggests that the fair-skinned peoples, having the most pronounced capillary circulation, would naturally best withstand Raynaud's disease. "Whole nations are pallid, others rubicund," he writes. "There is an antagonism between the amount of pigment and the degree of permanent distention of the vessels of the skin. The darker Teuton races have not nearly the same rich blood supply to the

hands and face as the fair Teutonic people." But if this be a predisposing cause for Raynaud's disease should not the negro be especially susceptible? Is he? Lee reports 3 cases of Raynaud's disease in the colored race, and there have doubtless been others; but it has not shown a marked preference for the members of this race.

The average age of the sufferers is a subject upon which there is a fair consensus of opinion, this being from twenty to thirty years in about 60 per cent of the cases recorded, although there is a general range of age from six weeks (Friedel) to eighty years. In this regard, however, it is to be noted that the diagnosis of Raynaud's disease in old people is extremely questionable and would have to be proven by tissue examination to establish that the case was not one of senile gangrene instead.

The temperament of the individual (which Raynaud considered of great importance) becomes a matter of less significance the more it is investigated. For every case showing the typical "neurotic" temperament described by Raynaud, there can be found one showing a normal balance. The same is true of the "previous condition of health," which has been so often remarked in medical literature to be "exceptionally good" in these cases. Investigation will show that this supposedly robust health of the victims of this disease is a myth in about 50 per cent of the cases on record. Diphtheria, pneumonia, jaundice, influenza, migraine, duodenal ulcer, tuberculosis, malaria, "intermittent fevers," ague, and syphilis, as well as numerous other diseases, all make their appearance in medical literature associated with that gangrenous phenomena known as Raynaud's disease. Even the exceptionally good health which Raynaud claimed for his cases becomes a matter for thought when we observe that heart and pulse irregularity were present in several of Raynaud's cases, of several others he says "the abdomen was hard and tumefied," several were habitually subject to venous stasis, and twice did he observe the disease associated with "a phlegmon of the neck, having for its point of departure the glands under the sternomastoid."

It is in the etiology of Raynaud's disease that we find the greatest difference of opinion. Syphilis is thought by some to be the true causal agent of Raynaud's disease, and some ten years ago this theory was widely held although it is not borne out by the usual blood reaction in these cases. While there are cases on record showing syphilis associated with the Raynaud phenomena, there are also a great number of cases giving negative histories for venereal disease and negative Wassermann tests. Indeed, so repeatedly is a negative Wassermann test found in these cases that one is led to wonder whether there may not be some relationship between such blood and Raynaud's disease itself. Does Raynaud's disease insure a negative Wassermann through some chemicophysiologic

process, or does syphilis immunize the tissues to whatever produces Raynaud's disease? The subject is worthy of thought. Syphilis is usually the first thought of the investigator of a case of Raynaud's disease and there are probably few of these cases today that are not tested out as thoroughly as possible for syphilis. Yet the percentage of positive Wassermann tests is markedly small. There are some cases giving a positive reaction, it is true, but the diagnosis of Raynaud's disease in such cases is open to question unless tissue examinations have been made, for the gangrene may be that of syphilis, and due to arteritis.

Malaria, defective glands, cold and exposure have all been suggested as the cause of Raynaud's disease. Lack of certain internal glandular secretions is regarded by some as the true cause. Improper food balance due to a shortage of vitamins, reacting on the general metabolic processes of the body, is also receiving serious consideration as a predisposing cause. Sexual excess and excitation are suggested as causes by several writers besides Raynaud himself, but this is a theory that is rapidly losing ground, as well it logically might. Not only do the histories of the recorded cases fail almost uniformly to bear out this theory of "sexual excess," but the average age of the sufferers (twenty to thirty years) is not an age most likely to feel the baleful effects of sexual excess even were this a fact, nor react unduly to sexual excitation. DeForest advances the theory that Raynaud's disease is due to a toxemia of some kind, and suggests copper as the toxic factor in several of his own cases, since these worked in copper. While the toxemia theory is not without argument, DeForest's paper on this subject loses much by the fact that in only 3 of the 17 cases he reports is the history given with sufficient detail to enable the reader to review the findings upon which the diagnosis of Raynaud's disease was based.

No one theory regarding the etiology of Raynaud's disease has caused more argument than that of malaria. While this is a theory often discussed in later literature, it is not a new one. It was one of the first theories advanced during the wave of investigation that followed the publication of Raynaud's original paper on symmetrical gangrene, and was for a time so well received that in 1899 Monro wrote, "The relationship which is now known to exist between malarial fever and Raynaud's disease was scarcely appreciated by Raynaud himself." This "known" relationship is not now so well known however. There are unquestionably many recorded cases of Raynaud's disease, especially among those from the Latin countries and our own southern states, that show evidence of malarial infection. There are cases on record in which the presence of malarial parasites has been demonstrated and which have been greatly improved by the use of quinin. But, on the other hand, there are unquestionably many other cases in which the patient had not and never had had malaria.

In view of this great difference of opinion regarding the symptomatology and etiology of Raynaud's disease, what are we to consider the truly essential features of this malady? Is there no common ground upon which all agree which may serve as the great essential of Raynaud's disease, according to which obscure gangrenes may be diagnosed and classified with some hope of progress toward determining the fundamental cause of this disease? Certainly the problem is merely complicated by confining modern investigators to a "classical picture," or by grouping under different names the basically similar gangrenes which do not conform in detail to this picture. Not only does this complication permit the inclusion under the heading "Raynaud's disease" of many gangrenes which, though not properly speaking Raynaud's disease, show the classic Raynaud phenomena; but it serves to classify under other heads many true cases of Raynaud's disease which fail to show the classic picture.

I think all who have read Raynaud's own researches must agree that to Raynaud himself the great essential feature of the gangrene he investigated lay not in its manifestations, but its mechanical cause. "A kind of gangrene which has its cause in a vice of innervation," he said, and it was this idea of a gangrene *due to a defective vasomotor mechanism* which was the basic thought behind his researches. It is this same idea of a gangrene due to vasomotor disturbance that should guide us in our diagnosis of Raynaud's disease today. Any gangrene which upon careful investigation is found not to be due to vascular obliteration, nor to organic disease, but which can be accounted for only by "innervation of the affected part" may be truly diagnosed Raynaud's disease, whether that gangrene be moist or dry, symmetrical or asymmetrical, involve only superficial tissues or the deep structures as well.

As to the cause of the innervation there are doubtless as many etiologic factors as in other nerve diseases. To discover which of these are truly causative factors is of course the problem at hand. But the problem of basic cause is not simplified by including as true causes all the predisposing conditions of this disease. Many of the theories of the etiology of Raynaud's disease, such as those of cold, exposure, trauma, and the like, deal with predisposing conditions rather than true causes. That these conditions are factors to be taken into account is true, but they are factors which set the stage for Raynaud's disease rather than produce it. It is essential that a clear distinction be drawn between these occasions for the onset of the Raynaud phenomena and the fundamental cause of this disease. Cancer is well known to develop by preference in some nonnormal portion of the body—some anatomical area weakened by too great activity, or by inactivity, or made especially susceptible by injury—but we know that the *cause* of the cancer lies deeper than these conditions. So with Raynaud's disease.

Any condition which interferes with the normal vasomotor activity of a given part may serve as the occasion for the development of Raynaud's disease, but the fundamental cause of this disease must be looked for elsewhere, probably in some constitutional abnormality or subnormality in the patient himself.

Of just what this abnormality or subnormality may consist is the great problem to be solved, but since no microörganisms nor disease-producing bacteria have yet been found in connection with Raynaud's disease, it seems highly probable that as a foundation for Raynaud's disease there exists some chemicophysiologic toxin, a conclusion strengthened by the complete sterility of the discharge from the diseased tissues in the case herein reported. Whether that toxin be the toxin of fatigue or of faulty metabolism, of overstimulated or understimulated glands, or of ill-balanced chemical elements we can only conjecture, for we know little of the toxins at best. But that some toxin is a causative agent, which manifests itself in some local area made especially susceptible by cold, injury, or any of the previously mentioned agencies, seems strongly indicated.

Following is the description of a case which the writer believes to be of unusual interest for several reasons: (1) Because it showed so few of the classic Raynaud phenomena and yet, being due to vasomotor disturbance, was unquestionably Raynaud's disease; (2) because parts of the bony skeleton of the foot were sloughed out in a discharge (corresponding no doubt to the "seropurulent liquid" mentioned by Raynaud), which was found upon examination to be *sterile;* (3) because postoperative dissection showed a remarkable adaptation of the crippled foot to the new demands made upon it by change in position for weight-bearing.

Case Record. The patient, a French Canadian woman aged twenty-six years, at the time of operation (disease had been in progress four years), was unmarried and a school teacher by occupation. Her chief complaint was a symmetrical gangrene involving the anterior half of the right foot internal to the third metatarsal, and the fourth toe of the left foot.

Her father and mother were still living and in good health with eight children in the family. There was no known history of constitutional disease. One aunt of the patient suffered badly from rheumatism.

The patient had had the ordinary diseases of childhood, but no malaria, typhoid or scarlet fever. Wassermann was negative. The patient states she was always in excellent health before this malady came on. She was not of a neurotic temperament, but very stolid. Her menses were always painful but regular. She has always lived a regular life, in a pleasant environment and has enjoyed her occupation.

Four years previous to the date of operation, the patient dropped a piece of ice on her foot, striking the second toe of the right foot. There was no abrasion. The toe became swollen and remained so for about a week. During that time it was painful, but the pain subsided with the swelling and the patient experienced no immediate trouble therefrom.

About three months subsequent to the injury pain developed in the right foot, centering around the second toe and radiating up the leg both fore

and aft. Pain did not subside when pressure was removed from the foot. There was no swelling at this time, but the toe was sometimes white and at other times red; pain was most severe when the toe was blanched.

This condition persisted for about four months, when the patient noticed that the pain and whiteness seemed to have spread to the great toe, which also became very painful; alternating local syncope and asphyxia developing concomitant with the pain. Later the asphyxia ceased; the great toe became white and cold and remained so.

It was approximately nine months after the initial injury that gangrene developed, and this developed not primarily in the second toe of the right foot, which had received the greatest previous injury, but in the great toe. It was at this time also that pain was first noted in the fourth toe of the left foot, which gave the same picture of alternating syncope and asphyxia before noted in the right foot.

The patient at this time consulted a surgeon who removed the right great toe. Following the operation a discharge began from the wound which suggested infection, but later bacteriologic examination of a similar discharge showed it to be free from pus cells and to consist only of serum and broken down detritus.

The wound healed gradually and was closed in about three months time. The pain, however, and the blanching of the second and third toes of the right foot and the fourth toe of the left foot continued with even greater severity. Almost a year after the removal of the right great toe gangrene developed on the internal border of the dorsum of the fourth toe of the left foot. This toe was then removed at its metatarsophalangeal articulation. The wound healed by primary union.

After the second operation the third toe of the left foot became painful, and alternating syncope and asphyxia set in. About four months after this the under surface of the right foot, opposite the distal heads of the first and second metatarsals, became swollen and almost unbearably painful. During the height of the swelling gangrene developed over this area. The tissues broke down and a great deal of fluid was discharged. An ulcer persisted for many months. The swelling gradually subsided and the ulcer finally healed. (End of second year.)

Increase in temperature of patient was not noted at any time.

About three months after the healing of the above-mentioned ulcer the foot became suddenly swollen and remained so for about three weeks. Pain was always present, which was no more severe at the time of the height of the swelling than before the swelling began. Gangrene developed over this area, and later another ulcer developed to the outside of the scar of the former one, about opposite the distal end of the second metatarsal. This gangrenous area broke down and a large quantity of fluid was discharged.

It was at this time that the patient first came on the writer's service. The abovementioned discharge was examined and found to be sterile and to contain fine granules of bone. A complete examination of the patient was made, including repeated serological tests. All laboratory findings were negative. Blood picture normal.

Physical Examination. The head, chest, cardiovascular system, and abdomen were negative and reflexes normal. The only positive findings were in the lower extremities.

The right foot was moderately swollen and the skin corrugated and of a brownish-gray color. A sinus about ½ inch in diameter, opposite the distal head of the second metatarsal, was noted. There was no evidence of active pus invasion, although a serous discharge was exuding from the sinus. An ulcer about the size of a half-dollar was present about the sinus. The second and third toes were blanched, cold, and swollen. There was

moderate retraction of these two toes. The third and fourth toes were moderately hypertrophied. The whole foot showed a tendency toward inversion, but the change in position and form of the foot was not comparable to that noted at time of operation two years later.

The left foot was apparently normal except for the absence of the fourth toe, although the patient complained of pain in the third toe.

Radiography of the right foot showed the following (Fig. 1): Absence of the great toe and the distal head of the first metatarsal; absence of the whole of the second metatarsal and atrophy of the proximal head of the first phalanx of the second toe, with absorption of calcium in the second and third toes; absence of the distal head of the third metatarsal and about one-quarter of its shaft, distally; moderate hypertrophy of the fourth and fifth metatarsals.

The left foot shows absence of the fourth toe and moderate absorption of the chalk from the distal head of the fourth metatarsal and the internal aspect of the fifth.

High amputation of the right foot was recommended, but was refused by the patient.

About ten months later the patient was seen by the writer at a time when the foot was enormously swollen and even more than usually painful. It was thought by the patient that the foot ought to be opened to let out pus. I refused to do so, however, since there was no fever and no constitional indication of active pus infection. Again high amputation was recommended but refused by the patient.

Within a few days a more extensive gangrenous area developed at the side of the second ulcer, and later on a great amount of serous material and granular substance was discharged through an ulcer in this area of gangrene. This ulcer remained open until operation was performed one year later (Fig. 2).

One year later a high amputation at the junction of the upper and middle thirds of the right leg was performed.

A second Roentgen ray picture (Fig. 3), made just before operation, revealed the progressive destruction of foot bones since the former picture, and change in general position of foot. The right foot shows almost entire destruction of bones of the medial-anterior portion of foot; absorption of phalangeal portions of fourth and fifth digits, and increase of calcium carbonate in the fourth and fifth metatarsals. Note also the changes in position of toes, their retraction, and the thickening of the superficial tissues of the foot as manifested by their heavy shadows in the Roentgen ray.

The left foot shows little change except in the loss of chalk in the fifth toe and the distal heads of the fourth and fifth metatarsals. Fig. 4 shows lateral view of right foot.

Externally the foot was much as it had been two years previous, except that it was more shrunken and darker. Two sinuses were present on the under surface of the foot, as were scars of other sinuses now healed.

The great difference in the right foot at time of operation and at time of examination two years previous lay in its conspicuous adaptation of form to function (Fig. 5). From the time the patient was first seen until the leg was amputated the patient had taken great care to dress the wound aseptically and antiseptically and had continued to attend to her duties as teacher. The weight had, of course, been transferred to the outer side of the foot. The foot had gradually changed its characteristics in response to the changed demands upon it and at time of operation it resembled a left foot more than a right one. In fact it looked like a left foot on a right leg. The little toe, having been forced to bear the weight usually resting on the great toe, had increased in size and assumed a more abducted position,

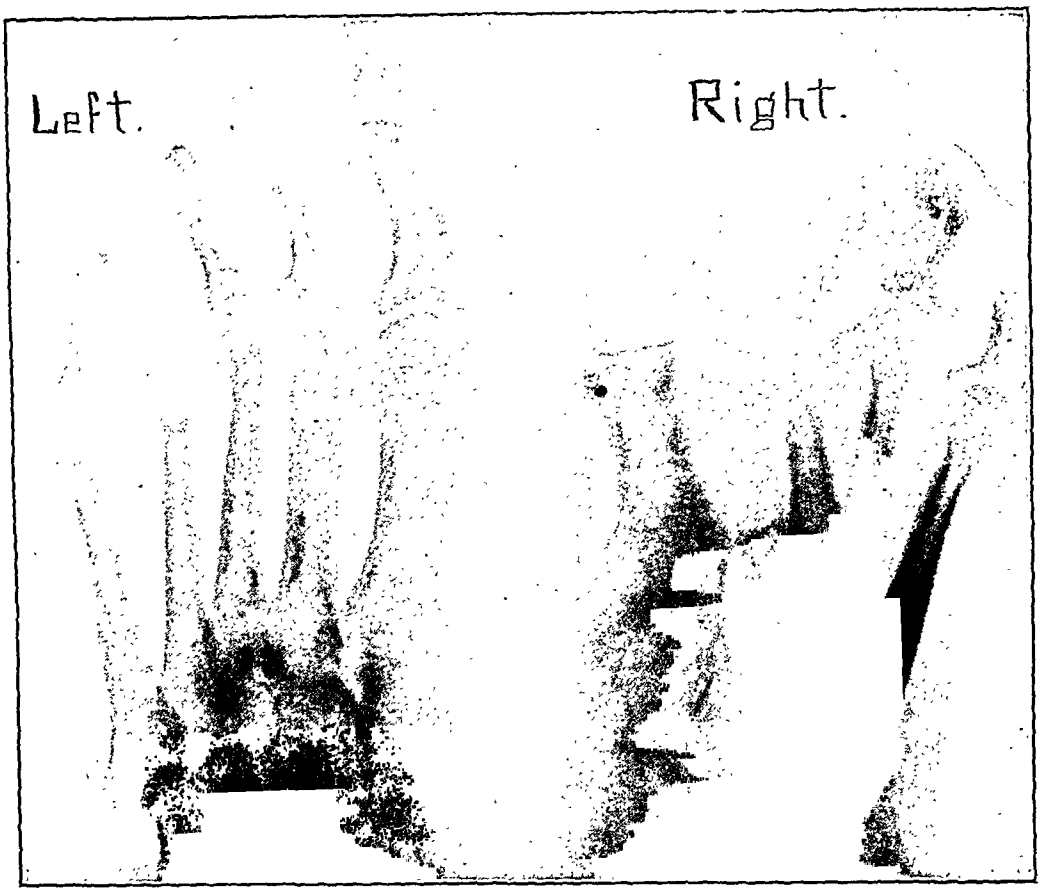


FIG. 1.—Roentgenographs of feet after Raynaud's disease had been in progress two years. Note: Right foot: Absence of great toe and distal head of first metatarsal (amputated); destruction by Raynaud's disease of the second metatarsal and proximal head of first phalanx of second toe; destruction of distal head of third metatarsal and about one-fourth of its shaft, distally; absorption of calcium carbonate in second and third toes; moderate hypertrophy of fourth and fifth metatarsals. Left foot: Absence of fourth toe (amputated) and foresigns of further extension of Raynaud's disease, as shown by absorption of chalk from distal head of fourth metatarsal and internal aspect of head of fifth.

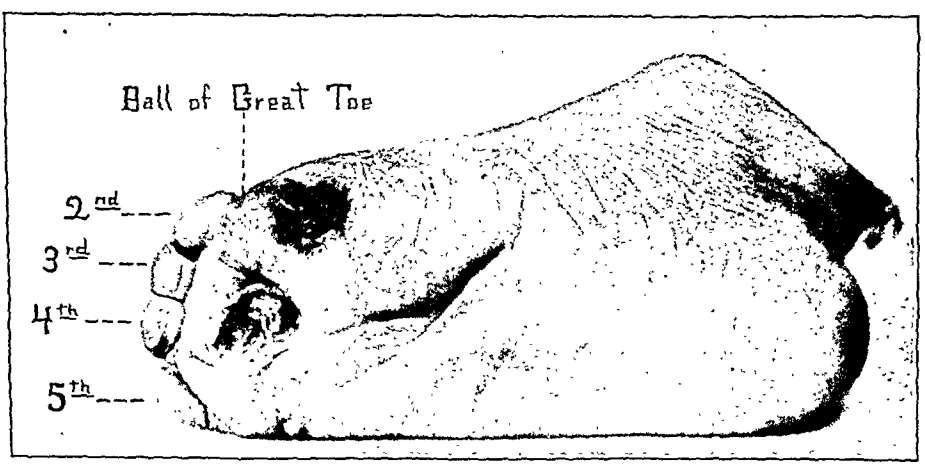


FIG. 2.—Right foot, plantar aspect, at time of operation.

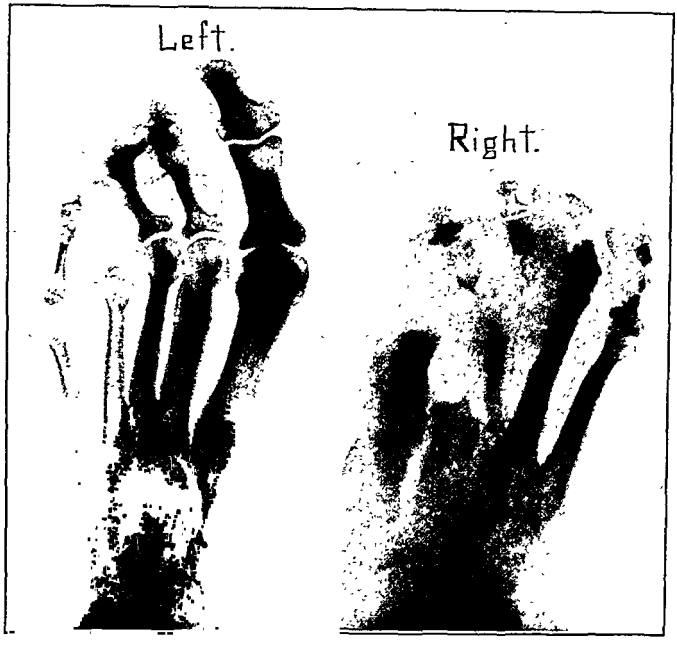


FIG. 3.—Roentgenograph taken two years after Fig. 1, showing progressive bone destruction. Note: Right foot: Entire destruction of bony skeleton of anterior-interior portion of foot; absorption of chalk from second, third and fourth toes; increase of chalk in fourth and fifth metatarsals; relative size of left and right foot; note also the abducted position and retraction of the second, third and fourth toes, and the denseness of the superficial tissues in the forepart of the right foot. Left foot: Further progress of Raynaud's disease over that shown in former roentgenograph is shown by absorption of chalk in the distal heads of the fourth and fifth metatarsals, the shaft of the fifth and the fifth toe.

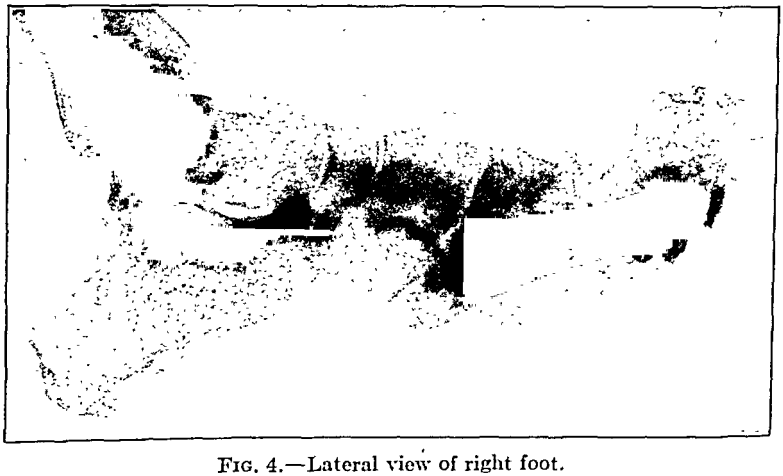


FIG. 4.—Lateral view of right foot.

until it suggested the great toe itself. This likeness was further emphasized by the shrinking and retracting of the other three toes to allow the fifth one to become the predominating digit. So marked was this adaptation of the right foot that, shown at a clinic, it was unanimously voted a left one.

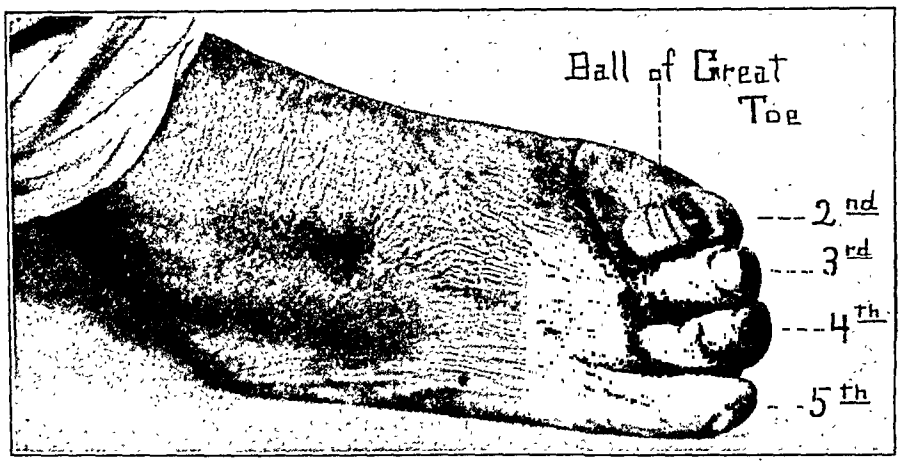


FIG. 5.—Right foot, dorsal aspect. Note change in relative development and position of toes, predominance of fifth toe and retraction and change of characteristics of the three inner toes, so that the fourth toe looks like a normal second and the second like a normal fourth. Adaptation of form to function.

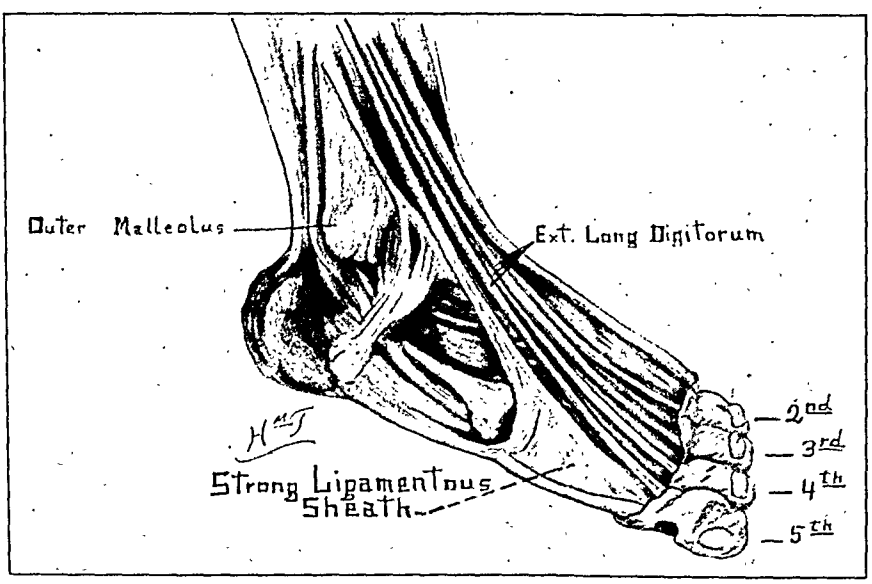


FIG. 6.—Dissection of foot shown in Fig. 5, dorsal aspect. Note adaptation of ligamentous structures to new functions. *Extensor longus digitorum*, well developed; tendons of peroneus tertius and abductor minimi digiti fused with thickened, plantar fascia to form hammock-like sheath for fifth digit as aid in its new function of weight-bearing.

Likewise the other toes of the foot had changed their characteristics, so that the fourth toe looked like a normal second, and the second like a fourth.

Postoperative dissection showed further evidences of this adaptation of form to function in the development of the ligamentous structures of

the foot. In the under surface of the foot normal relationships were entirely destroyed in the medial-anterior portion, and it was impossible to identify the various muscles and tendons still remaining. In the dorsum of the foot, however, both muscles and ligaments were intact and showed marked compensatory development (Fig. 6). The tendons of the extensor longus digitorum were very well developed, accounting, no doubt, for the retraction of the three inner toes. The slip inserting into the fifth toe was also unusually well developed, but this toe had been saved from retraction by other ligamentous adaptations. The tendons of the peroneus tertius and the abductor minimi digiti had fused with the plantar fascia of the foot, which here showed marked thickening, and formed a strong, ligamentous sheath about the outer and under surfaces of the fifth digit, which apparently reinforced this digit for its new function as a great toe.

Such a marked adaptation in so short a time indicates a remarkable vitality in the undiseased portions of this foot, and is worthy of note.

Dissection also revealed important findings regarding the veins, arteries, and nerves. The bloodvessels were atrophied to such an extent that they were in places indiscernible, the atrophy being less marked the higher they extended up the leg. There were no evidences of venous or arterial obstruction. The nerves, on the other hand, seemed very large and were encased in fat.

Up to the present date (two years after operation) there has been no evidence of further disease of the right limb. For some months following operation patient complained of pain in the left foot, but this gradually subsided and she has had no further discomfort therefrom to date.

Summary. 1. Investigation of the basic cause of Raynaud's disease, and its cure, is hampered by the narrow limitations of the classical picture.

2. The guide to diagnosis of Raynaud's disease should be the evidence of defect in the vasomotor mechanism rather than conformity of clinical manifestations to the phenomena as described by Raynaud.

3. Thus, all gangrenes that can be accounted for by gross vascular obliteration, or other nonvasomotor causes, should be definitely excluded as "Raynaud's disease" even though they show the classic Raynaud phenomena; and, all gangrenes that give evidence of being due to vasomotor disturbance should be included as "Raynaud's disease," whether they be moist or dry, symmetrical or asymmetrical, involve only superficial tissues or the deep structures as well.

4. A chemicophysiological toxin is suggested as the cause of Raynaud's disease.

5. The record of a case of Raynaud's disease showing extensive bone involvement is of interest for several reasons: (1) Because it showed so few of the classic Raynaud phenomena and yet was unquestionably Raynaud's disease; (2) because parts of the bony skeleton of the foot were sloughed out in a discharge which was found to be sterile; (3) because of the remarkable adaptation of form to function displayed by the crippled foot.

A bibliography of the subject will be furnished on request.

THE RESPONSE OF THE NORMAL HUMAN STOMACH TO VARIOUS STANDARD FOODS AND A SUMMARY.

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In this communication we wish to summarize the results of the investigations which we have carried on for some years on the behavior of foods in the normal human stomach. While it is true that we have certain conceptions regarding the digestion of the various groups of foodstuffs, our knowledge on this subject has been largely based on Roentgen ray observations on the study of individuals with gastric fistulas, or otherwise traumatized, or by means of a method; namely, the old form of intubation, which did not permit of satisfactory study of the entire period of digestion. By recourse to fractional analysis we were able to follow the digestion of various foodstuffs throughout the entire period of gastric digestion and were enabled to study precisely the important points regarding their evolution. This series of studies, performed on a large number of normal persons, all of whom were completely habituated to the use of the tube, represents, to our knowledge, the first complete series of investigations covering the action of all the different varieties of foodstuffs in the normal human stomach. These experiments, extending over a period of six years, were performed under the best possible conditions and present a basis for the interpretation of pathological stomachs when examined under similar conditions. It was with this object in view; namely, to obtain an exact basis for the interpretation of pathologic data as well as to work out the exact influence of the various types of food in human digestion that this investigation was carried out. In this paper we wish to briefly point out some of the cardinal points in these investigations. In this series of studies, we examined, in connection with each foodstuff, the fast and slow stomachs which we recognized as variations in normal types. We also recorded the exact evacuation time of each particular foodstuff and the highest total acidity which was observed during digestion, and in many instances these studies were extended to include pepsin determination as well as formal titration. The quantities of foods were weighed and the chemical analyses were performed, in all instances, by chemists especially skilled in this work.

In a series of seventy complete experiments on twenty-five different subjects with 100 gm. of beef products which included

roast beef, rare, medium and well done; hamburg steak; sirloin steak; stewed beef; dried beef; tongue; corned beef; bologna; calves' liver; frankfurters; sweetbreads, and tripe; we obtained an average evacuation time of two hours and thirty-five minutes in the fast type of stomach and three hours and twenty-five minutes in individuals with the slow stomach. These gave a total average of approximately three hours for all varieties of beef products, and the average total acidity at the height of digestion for all forms of beef products was 120. It was interesting to note that roast beef appeared to be handled with practically the same ease whether rare, medium or well done, and no advantage was found in the evacuation of hamburg steak over the same weight of roast beef under identical conditions. Dried beef and corned beef presented similar reactions to roast beef. Tongue, however, was less readily digested than dried beef. In the study of the passage of meat from

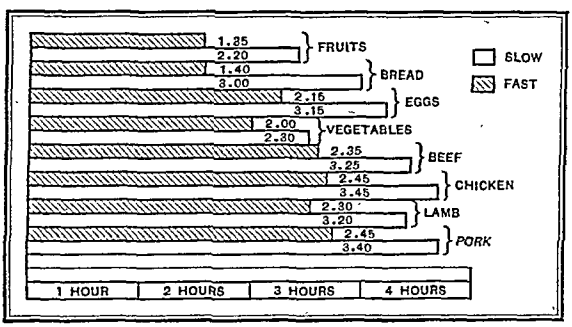


CHART I

the stomach into the duodenum, it was noted that there is a separation of the different parts of the meat which empty separately. The finely divided portions which settle to the bottom are affected first; this is followed by the coarse fibrous material and finally, the fatty material.

Thirty-one different tests on ten different subjects with pork products were made. These included roast pork; sausage; fried, boiled, minced and baked ham; bacon; liver and bacon; scrapple, and pork chops. In this group, the average evacuation time for rapid stomachs was two hours and forty-five minutes and for slow stomachs, three hours and forty minutes, showing a general average for pork products somewhat in excess of the period found with beef products. The average total acidity observed at the height of digestion was 117, while liver and bacon required about the same period of digestion as roast beef; pork chops and fried ham required a considerably longer period. Bacon alone required considerable time (four and a half hours) as compared with the average evacuation time of the rest of the food products.

Fourteen examinations were made of lamb products including roast lamb, stewed lamb, lamb chops and sheep's brains. In this group the average evacuation time for rapid stomachs was two and a half hours, and for slow stomachs, three hours and twenty minutes, showing a general average evacuation time similar to beef products; but the average total acidity was considerably higher; namely, 135 as compared with 120 for beef products. It is evident from this series that digestion of meat products generally, at least for 100 gm., is approximately in the neighborhood of three hours, and the highest total acidity in the neighborhood of 120, figures

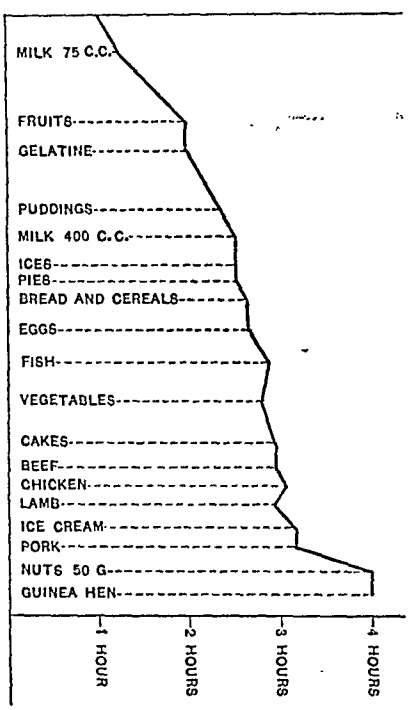


CHART II

which we have before pointed out as being construed by clinicians as high acidity.

Ninety experiments were performed on eighteen different subjects to test the response to eggs. Every variety of egg preparation was used including the raw white, the raw yolk, whole raw eggs soft boiled eggs, hard boiled eggs, scrambled eggs, fried eggs, plain and spanish omelet, deviled eggs, poached eggs, pickled eggs, duck's eggs, turkey's eggs, frozen hen's eggs, cold storage eggs and egg combinations such as milk and eggs, bacon and eggs, frizzled beef and scrambled eggs and the raw whites with orange juice. In each instance two eggs were used as an experimental meal, and it was noted that for all egg preparations the fast stomach showed an average evacuation of two hours and fifteen minutes, and the

slow stomach showed an average evacuation of three hours and five minutes, and for the whole series of egg preparations the average of the highest acidity was 80. Briefly, therefore, eggs give rise to less stimulation than meat and leave the stomach sooner, and show high combined acidities particularly through the early period of digestion. The raw egg white leaves the stomach more rapidly than any other form of egg preparation and produces only a moderate secretion of gastric juice in individuals of the hypersecretory type, a secretion which is only apparent toward the end of digestion. If distilled water is added to egg white, however, a more pronounced stimulation of secretion is produced. The egg yolk, on the other hand, produces a perceptible secretion and

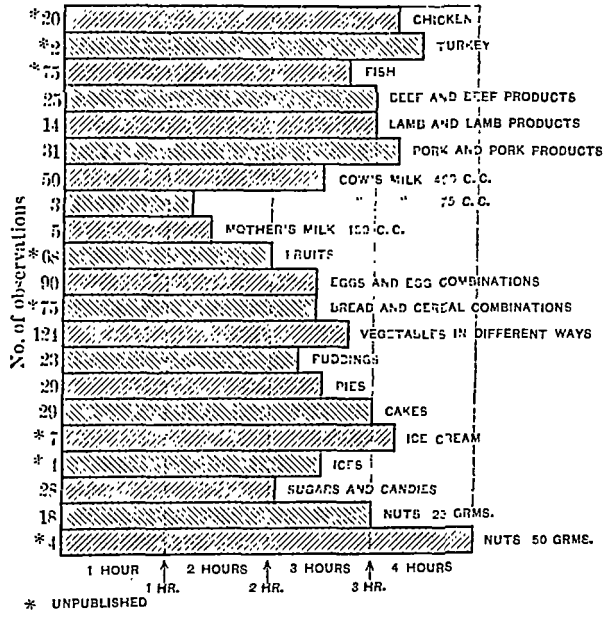


CHART III

requires a longer period for evacuation. For instance, in three subjects the average evacuation time for the raw white was one and a half hours, while in the same number of cases the average evacuation of the raw yolk was two hours and thirty-five minutes. Hard boiled eggs required only ten minutes longer in subjects of the rapid evacuation type than did soft boiled eggs. The average period for soft boiled eggs was two hours in rapid stomachs. In the same group, the average evacuation time for hard boiled eggs was two hours and ten minutes, while the acid response was similar in both. Fried eggs required only two hours and fifteen minutes. The eggs of the duck and turkey were handled in much the same way as hen's eggs. It is apparent, therefore, that eggs give rise

to a perceptible secretion even though it is less than that encountered with meat. Likewise a shorter evacuation period explains its value in many conditions associated with delayed evacuation.

One hundred and twenty-four experiments on thirty different kinds of vegetables were made on twenty-five normal men. The average evacuation time for all vegetables in the fast stomach was two hours and for the slow stomach, two and a half hours; while the average total acidity for the former was 70 and for the latter 77. This series included potatoes, (boiled, creamed, baked, mashed, fried) sweet potatoes, dasheen, cassava, oyster plant, beets, carrots, parsnips, radishes, turnips, beans, lentils, peas, asparagus, cabbage, coleslaw, sauerkraut, cauliflower, celery, lettuce, spinach, onions, cucumbers, squash, tomatoes, mushrooms, barley, rice, corn, hominy. The samples which were examined for fractional analysis were also examined microscopically with the view of determining the degree of disintegration and the extent of starch digestion and other changes. Vegetables fed in raw condition showed slow disintegration of the cells and cell masses. This was particularly noted for raw carrots, celery, tomatoes, lettuce, cabbage and cucumbers. Boiled carrots and cabbage showed much more complete disintegration, and this was true of most boiled vegetables; namely, white and sweet potatoes, turnips, squash, peas and dasheen. Somewhat less rapidly broken up were fried potatoes, spinach, string beans, oyster plant, parsnips, baked beans, asparagus, beets, sugar corn and cauliflower. The starchy vegetables such as potatoes were found to be considerably affected by salivary digestion. Sweet potatoes in whatever form remained longer in the stomach than white potatoes, and this was true of the dasheen. Oyster plant required the same period of time as white potatoes. Boiled beets and raw carrots left the stomach rather rapidly in from one to two hours while boiled carrots required a distinctly longer period. Radishes in small amounts left the stomach with great rapidity (one and a quarter to one and a half hours), while baked beans remained for a somewhat longer period in the stomach than most vegetables, requiring three and a half hours in the slow emptying type. Cabbage left rapidly as well as asparagus, asparagus leaving in one and a half hours, raw cabbage in one hour and forty minutes; and raw lettuce likewise showed an extremely rapid evacuation time of slightly over one hour. The addition of sugar, vinegar or oil, however, delayed the evacuation of lettuce. Spinach remained in the stomach distinctly longer than most vegetables. Raw tomatoes left earlier than boiled tomatoes. In two individuals with fast stomachs, raw tomatoes left in one hour and ten minutes, while the slow stomach handled them in one hour and fifty-five minutes. Canned stewed tomatoes, however, in the slow stomach required three hours. In general we noted that raw vegetables

which are low in protein such as carrots, celery, tomatoes, cabbage, lettuce and cucumbers left the stomach rapidly, developing moderately high acidities with but little combined acidities and left the stomach without great change in appearance. Boiled vegetables, however, showed much more rapid and complete disintegration. Furthermore, it is to be noted that vegetables high in starch such as potatoes may show in certain cases very considerable starch digestion before leaving the stomach so that the starch reaction is difficult to obtain.

Our results on milk are of particular interest. In these tests, we were fortunate in having the coöperation of a man who had the unique power of emptying his stomach completely at will or of giving small samples of the stomach contents at any desired stage of digestion. By making use of this man's skill as a regurgitator, we were able to demonstrate a number of things regarding the curdling and digestion of milk which would have been impossible without his aid. Brenneman[1] has also employed a regurgitator in the study of curd formation. However, his subject did not do "fractional" regurgitating.

Raw whole milk curded in rather hard, firm, white curds, possessing a rather rubber-like consistency. About one hour after the milk entered the stomach the maximum curd formation was noted. It was apparent that large curds were produced through the coalescing of smaller curds. At the one hour-period curds as large as a man's thumb and 15 gm. in weight were demonstrated. When the milk was boiled for five minutes the curds produced were yellow in color and small, soft and fine in appearance. From boiled milk the largest curds were no larger than a small pea. Curds of this character were more digestible than the raw milk curds and left the stomach sooner. Inasmuch as boiling for five minutes does not alter in any material way the nutritive or growth-promoting properties of the milk (except the antiscorbutic value which is lowered) it would seem that boiled milk should be given the dietetic preference. When raw skimmed milk entered the stomach, particularly tough, hard curds of large size were formed. The curd formation began in about a half minute and inside of five minutes the curds had coalesced to form individual curd masses as large as the thumb of a man. Our regurgitator complained of a heavy feeling in his stomach soon after drinking skimmed milk and had more difficulty in delivering samples of skim milk curds than curds of any other character. This was due to their firm, unyielding character. The curds from boiled skim milk were not as large and tough as were those from the raw skim milk nor as small and soft or as easy of digestion as those from the boiled whole milk.

1 J. Am. Med. Assn., 1913, 60, 575; Arch. Pediat., 1917, 34, 81.

Inasmuch as the whole milk contained 4 per cent of fat, whereas the skim milk contained only about 0.5 per cent, it would seem that the character of the curd formed from boiled milk is regulated to a degree upon the quantity of fat present.

The influence of fat was also shown in our studies on cream. It was apparent in these tests that the character of the milk curds was influenced in a direct way by the fat content, that is, the more fat, the less curd. Furthermore, the curds were smaller and softer the higher the fat concentration. With 40 per cent cream, for example, no curds were formed during the first half hour. Moreover, the largest curds were only about the size of the head of a pin and they did not coalesce to form larger curds as they did with milk of low fat content. We also noted that milks of high fat value left the stomach slowly. In fact, 475 cc. of material was returned from the stomach two and a half hours after drinking 500 cc. of 40 per cent cream. An exception to the above rule was found in the case of skimmed milk (0.5 per cent fat) which left the stomach somewhat slower than raw whole milk (4 per cent fat). This finding was attributed to the fact that the curds of the skim milk were tough and disintegrated but slowly in the stomach.

When $2\frac{1}{2}$ gm. of sodium bicarbonate was added to 500 cc. of raw whole milk, the curds produced were smaller and softer than were those formed in the absence of the bicarbonate. Curd formation began in about five minutes although the stomach contents were distinctly alkaline for a half hour. Boiled milk left the stomach sooner than the bicarbonate milk and the curds were smaller and softer.

The curds of pasteurized milk were found to be intermediate in character, between the curds of raw and boiled milk, with a tendency to resemble more closely the curds of raw milk. The pasteurized curds, however, did not coalesce to such an extent as did the raw milk curds.

If water was drunk before the ingestion of milk, there was no particular alteration in the curdling tendencies of the milk, except that the curds were somewhat softer and the maximum sized curds were smaller than when no water was taken. The extra volume of fluid in the stomach may have prevented the coalescing of small curds to form large ones.

Temperature had no material influence upon curd formation. Milks which were considerably below body temperature curdled a little more slowly but the delay was not conspicuous. We demonstrated that milks at 20° C. began to curdle in one to two and a half minutes, whereas milks at 37° C. began to curdle after the lapse of only a half minute.

When a mixture of 80 per cent boiled whole milk and 20 per cent raw whole milk was drunk the curds were similar to those obtained

from raw whole milk. The soft, fluffy, yellow curds of boiled milk were never in evidence.

The question of rapid and slow drinking of milk was also investigated. In these tests it was found that milk drunk rapidly left the stomach sooner and produced a smaller curd mass than did milk which was drunk slowly or sipped.

It was interesting to observe the response of the stomach to pies, cakes and puddings, and here again a study was made of the acid responses and evacuation time of nearly fifty different preparations. Twenty-nine experiments were performed on pies including pumpkin, mince, lemon meringue, raisin, coconut custard, cherry, peach, apple, and rhubarb. The findings in this series of cases were for the pie crust an average evacuation time of two hours and fifty-two minutes and for the inside of the pie two hours and twenty-six minutes. The average highest acidity developed with the pie crust was 90, while the average highest acidity for the contents was 103. Twenty-nine experiments were likewise performed on cakes including angel food, devil's food, fruit cake, lady fingers, crullers, doughnuts, cream puffs, short cake, cinnamon bun; and here again the average total acidity was 90 and the average evacuation time three hours and two minutes. Twenty-three experiments were performed on pudding including Indian, cornstarch, chocolate pudding, brown betty, cabinet pudding, rice, rice and raisin, cup custard, plum, bread, tapioca, and gelatin. The average total acidity was 92 and the average evacuation time two hours and eighteen minutes. Comparing the highest total acidities, therefore, for pudding, it was 92, for pie 90 and for cakes 90. Making a comparison of the type of food, it is evident that puddings are handled more readily than pies and cakes, the average evacuation of puddings being two hours and eighteen minutes, the average for pies, two hours and thirty-nine minutes and the average for cakes, three hours and two minutes. A number of interesting observations were made in this connection. Custard pies have a fairly high acid combining power, while the fruit pies have a low acid combining power. Angel's food cake remained distinctly longer in the stomach than devil's food cake and developed a higher total and combined acidity. Strawberry short cake left in from three to three and a quarter hours and developed a high acidity (127). The highest total in combined acidities was occasioned by Indian pudding, bread pudding and cup custard, all of which are high in protein. Gelatin, on the other hand, produced little acid stimulation and left the stomach rapidly.

A study was made also of sugars and candies, thirty-two experiments being performed with glucose, cane sugar, maple sugar, chocolate creams, chocolate, caramels, marshmallows, popcorn. In this connection, here again, it is evident that large amounts of

either cane sugar or glucose (100 gm.) markedly depress secretion and delay evacuation, while small amounts (10 gm.) do not appreciable affect either. It is for this reason that candies should be eaten after, rather than before, meals, but in any appreciable quantity they can delay the appearance of the secretion. Tables and curves summarizing our data on the motor and secretory activities of the normal stomach are reproduced herewith. The evacuation times and acidity values are given in round numbers in order to facilitate comparisons.

TABLE I.—MOTOR TABLE SHOWING EVACUATION TIME FOR VARIOUS ARTICLES OF DIET.

Article of diet (100-gram portions unless otherwise stated).	Number of observations.	Evacuation time (hours and minutes). Type of stomach.		
		Rapid emptying.	Slow emptying.	Average.
Beef and beef products	25	2.35	3.25	3.00
Lamb and lamb products	14	2.30	3.20	3.00
Veal:				
(*a*) Market	7	...	...	2.50
(*b*) "Bob"[1]	7	...	...	3.20
Pork and pork products	31	2.45	3.40	3.15
Chicken[1]	20	2.45	3.45	3.15
Turkey[1]	2	3.00	3.45	3.30
Guinea hen[1]	2	...	4.00	4.00
Fish[1]	75	...	...	2.50
Milk:[1]				
Cows':				
400 cc.	50	...	...	2.30
75 cc.	3	...	...	1.15
Mothers':				
150 cc.	5	...	...	1.40
225 cc.	2	...	...	2.25
Gelatin[1]	5	...	...	2.00
Egg and egg combinations	90	2.15	3.15	2.40
Vegetables prepared in different ways	24	2.00	2.30	2.50
Fruits[1]	68	1.35	2.20	2.00
Bread and cereals[1]	75	...	...	2.40
Cakes	29	...	...	3.00
Pies	29	...	...	2.30
Puddings	23	...	...	2.20
Sugars and candies	28	...	...	2.05
Ice cream[1]	7	...	..	3.15
Ices[1]	4	...	...	2.35
Nuts:[1]				
(*a*) 25 gm.	18	..	...	3.00
(*b*) 50 gm.	4	...	..	4.00

[1] Unpublished data.

The above are the complete tables up to date as about to be published by Rehfuss, Bergheim and Hawk.

TABLE II.—ACIDITY TABLE SHOWING HIGHEST TOTAL ACIDITY FOR VARIOUS ARTICLES OF DIET.

Articles of diet 100-gram portions unless otherwise stated.	Number of observations.	Highest total acidity (average) (cc. N/10 alkali to neutralize 100 cc. juice).
Beef and beef products	25	120.0
Lamb and lamb products	14	135.0
Veal:[1]		
(a) Market	7	140.0
(b) "Bob"	7	110.0
Pork and pork products	31	120.0
Chicken[1]	20	125.0
Turkey[1]	2	140.0
Guinea hen[1]	2	110.0
Fish[1]	75	130.0
Milk:[1]		
Cows':		
400 cc.	50	100.0
75 cc.	3	45.0
Mothers':		
150 cc.	5	60.0
225 cc.	2	90.0
Gelatin[1] (fruit juice preparations)	5	70.0
Egg and egg combinations	90	80.0
Vegetables prepared in different ways	124	75.0
Fruits[1]	68	90.0
Bread and cereals	75	80.0
Cakes	29	90.0
Pies	29	90.0
Puddings	23	90.0
Sugars and candies	28	70.0
Ice cream[1]	7	105.0
Ices[1]	4	65.0
Nuts[1] (25 to 50 gm.)	22	100.0

[1] Unpublished data.

The above are the complete tables up to date as about to be published by Rehfuss, Bergeim, and Hawk.

It is apparent from these studies that there are considerable gradations in both acid output and evacuation time with regard to even the separate groups. After this series of examinations was made it was suggested that we test the direct effect of emotion and psychic disturbance on individuals, and this we have attempted to do in rather an extensive fashion. In one individual who was about to undergo an examination in chemistry 100 gm. of fried chicken was tested out and the same quantity was again given after he was relieved of this strain. The emotional strain induced by an examination which he was uncertain of passing was sufficient to prolong, or rather retard, the digestion of chicken for over two hours and produce very high acidity. In a series of experiments on the effect of psychic influences, there was no question that the sight of a table which was properly laid out gave rise to a distinct secretion of gastric juice in normal individuals, while the sight of the same food, improperly prepared and poorly served, failed to give rise to an appetite secretion. Odor gave rise to less stimulation than the sight of food. Even the sound and thought of a frying steak gave rise to gastric secretion; however, it was to be noted that the ultimate utilization

of protein thus prepared in an unpalatable manner has not been found to be appreciably less than that of the same diet served under the best conditions. Anxiety and mental strain, however, will markedly retard gastric digestion.

Summary. In this series of studies, therefore, it is apparent that there is a certain characteristic response for each variety of foodstuff. The results also serve to emphasize the ability of the normal stomach to satisfactorily handle a great variety of foods. In each particular instance, the stomach has a certain amount of work to do which in health it does in a highly characteristic manner. The digestion of meats is one of great interest, and the same thing is true regarding the digestion of fresh vegetables. With the raw vegetables, however, digestion is much more of a mechanical procedure, but in each instance the test of a normal stomach is the ability of that stomach to handle these substances in characteristic fashion. Even in these experiments it was apparent that functional diseases almost always resulted in either a delay in evacuation or in a rise in the acid secretion or again in a failure of the stomach to react rapidly to the food in question. The exact significance of these findings we hope to work out in future experiments.

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SOME REASONS FOR POOR RESULTS FOLLOWING GASTRO-INTESTINAL SURGERY.[1]

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There are many evidences in the literature that those who from time to time reëxamine patients after abdominal operations find the

[1] Read at a meeting of the Section of Gastroenterology and Proctology of the American Medical Association, May 29, 1925.

results of surgical intervention most disappointing. There is, furthermore, evidence in abundance to show that the reason operation fails to afford the patient symptomatic relief is that the fundamental cause of the trouble has not been discovered and removed.

Some time ago Rosenow[1] demonstrated the relationship between foci of infection, such as occur in the teeth and tonsils, and certain gastrointestinal lesions. An affinity was shown to exist between the organisms of such foci and alimentary structures—notably between the streptococcus and the gall bladder. Nakamura[2] has also shown experimentally that a distinct relation exists between certain foci of infection and ulcer of the stomach. This same relation appears to exist with lesions elsewhere in the gastrointestinal tract.

Although the exact relationship between disease changes in one section of the gastrointestinal system with those in another is not known, the feeling is growing that *isolated* lesions in any one organ rarely occur. Biliary disease, for instance, is invariably associated with disease in other viscera, especially in the liver, pancreas, appendix and colon. The association of hepatitis with chronic biliary disease and gastroenterocolitis has recently been vividly demonstrated by Heyd,[3] Stockton,[4] Tietze[5] and others. It is essential, therefore, from the etiologic standpoint, that we view the liver, pancreas, gall bladder and gastroduodenal segment as one physiologic and pathologic system.

In addition to infection, other etiologic factors that must be considered in effecting a cure in chronic gastrointestinal disease are visceroptosis, intestinal stasis, cecal dilatation, cecum mobile, asthenia, neurasthenia and familial predisposition, all of which are important predisposing conditions.

Appendicitis. A review of the literature of chronic appendicitis reveals a wide divergence of opinion regarding the nature, significance and treatment of that condition. Cabot[6] says he has *never yet* seen a patient whose symptoms he could attribute to chronic disease of the appendix. Among 15,000 cases of chronic dyspepsia he found that 12,600 owed their symptoms to extragastric lesions, but of these he does not consider chronic appendicitis as even a possibility. Mayo, Brewer, Deaver, Lichty and others, on the other hand, believe that chronic disease of the appendix is a frequent cause of gastrointestinal symptoms. There can be no question, however, that chronic appendicitis must often be considered an end result, and it must be determined whether the patient's symptoms may not be due to associated lesions, outside of the gastrointestinal tract, or to functional or systemic diseases that will continue to give symptoms after the appendix has been removed. Indifference to this fact unquestionably swells the already discouraging numbers of appendectomized patients who have secured no relief from their operation. Lichty,[7] for example, reports that of 517 patients sub-

mitted to surgery without any relief, 243 were operated upon for chronic appendicitis. Many of the surgical statistics present a lower percentage of failures, but this can be attributed to the fact that frequently the success of the operation was determined at the time of the patient's discharge from the hospital, and the cure at that time was more apparent than real. Deaver,[8] in speaking of the failures in a group of cases which he reports, says they were partly due to pathologic conditions, unrecognized because of faulty study and faulty exploration. Whiteford[9] writes: "Many patients whose abdominal ailments are now diagnosed as chronic appendicitis, suffer from symptoms of widely varying causation, and for these symptoms the appendix is not responsible." The symptoms attributed to the chronic appendix are not explained by the pathologic findings, and are not cured by removal of the appendix. Furthermore, the habit of attributing abdominal discomfort of obscure origin to the appendix hinders investigation into the causes of abdominal pain.

In considering the indications for operation the history and physical examination, and if accepted with caution the Roentgen ray evidence, serve as our best guides. Roentgenographic evidence alone, however, no matter how convincing, should never serve as an indication for operation. I think it may be conservatively stated that the mere procedure of removing the appendix will invariably fail to relieve the neurotic of his gastrointestinal symptoms, especially if he has a colitis, and the visceroptotic, particularly those with a mobile cecum and intestinal stasis, all of whom present a picture of chronic appendicitis.

The probabilities of cure from appendectomy—and, of course, acute appendicitis is not being considered—will be in direct proportion to the accuracy with which the occurrence of previous acute attacks can be determined. In summing up this question, Whiteford declares that: "In the interests of surgeons and patients the diagnosis of chronic inflammation of the appendix as a condition requiring operation should be abandoned."

Ulcer. While for the surgical treatment of peptic ulcer the percentage of failures may not be as great as that for chronic appendicitis, there nevertheless are many patients who should receive greater relief following operation than they do. Although statistics from reliable sources vary widely, they indicate that from 15 to 40 per cent of ulcer operations are failures. Excluding improper and imperfect surgery, which will not be discussed, the factors entering into the disappointing results are manifold. W. J. Mayo attributes 5 per cent of surgical failures in ulcer to faulty dietetics after operation. Inasmuch as most recurrences take place within two to three years after the operation, persistent adherence to medical treatment should be continued at least this long. Dr. Finney, a former President of the American Surgical Association,

struck a high note when he said: "Let us never forget that a surgeon's whole duty is not done when he sends a patient home with a healed wound. It is possible to have as an end result a perfectly healed wound with permanently impaired function."

Inasmuch as chronic ulcer of long standing has probably little tendency to heal and stay healed under medical management, the proper surgical treatment, provided adequate preoperative and postoperative attention is given the patient, should hold forth greater promise of ultimate cure. The surgeon's contention, however, that most ulcers even in their early stages should be treated surgically, is not borne out by the facts. The evidence tends rather to show that the recurrent character of the lesion depends on the formation of a new ulcer, or ulcers, and not, as a rule, on the breaking down of the old ulcer. The postoperative, as well as the medical, recurrence of ulcers suggests, as Smithies pointed out some years ago, that in treating ulcer one is dealing with only a local complication of a systemic or constitutional disturbance, to which must now be added a vital factor in the etiology of such disturbances, namely, infection. To our knowledge of the relation of focal infection as a cause of peptic ulcer, Hayden[10] has recently reported additional proof. Forty-five rabbits were injected with cultures from dental foci in 8 patients with peptic ulcer; 53 per cent of the animals developed peptic ulcer lesions, and the duodenal lesions were limited to the duodenal bulb just as they are in man. In view of facts such as these, it appears that the source of infection and the constitutional abnormalities should receive first attention. In connection with the latter, Devine[11] advances the conception that abnormal development or irritability or disease of the notoriously labile sympathetic nervous system can alter the postural tone of the gastric and duodenal muscle controlling the emptying time of the stomach, and the natural protective regurgitation which controls acidity, and may thus initiate a train of circumstances which may eventually result in ulcer. In addition to eradicating foci of infection, effective treatment of peptic ulcer must, therefore, be directed toward such underlying and predisposing conditions as nervous instability, overwork, worry, constipation and dietetic and other indiscretions. Recognition of these principles offers the only hope of an actual cure. It is plainly evident that the operation for gastric or duodenal ulcer must be regarded as only an incident in the treatment of the patient. As is the case with chronic appendicitis, cholecystitis, hepatitis and pancreatitis, ulcer is only an end result and, helpful as surgery is for this end result, the ultimate cure must depend on further enlightenment as to the cause and pathology of these ulcers.

GALL BLADDER. In discussing the results following surgery on the biliary tract, we are again confronted with a formidable number of unimproved cases. Moynihan[12] reports that one-fifth of the

total number of patients suffering from cholelithiasis, upon whom he operated, had previously submitted to operation for this condition. Deaver[13] states that 4 to 8 per cent of patients operated on for biliary disease return because of recurrent symptoms; of these, 80 per cent have returned following cholecystostomy. Judd[14] reports, from the Mayo Clinic, that, during the year 1920, 1022 operations were performed on the gall bladder and ducts; of this number 114 were operations necessitated by the recurrence of symptoms after the first operations. In considering the etiology of disease of the biliary tract, first and foremost arises the question of infection, which we have already discussed, due emphasis being laid on the demonstrated affinity of the streptococcus for the gall bladder. The necessity, then, of tracing these organisms to their lair in the teeth, tonsils, sinuses, colon and elsewhere becomes apparent. Moynihan emphasizes the fact that a lurking area of infection anywhere in the body may be responsible for the recurrence of stones in the gall bladder, liver or ducts. He also attributes recurrence to an increased cholesterol content of the blood, and notes that 60 per cent of gall-stone patients are hypercholesterolemic, and in the remaining 40 per cent the blood cholesterol shows high normal values. Such findings have been confirmed by other investigators; there are, thus, strong indications that this substance may be the basic cause of the formation of these stones. Recognition of this factor is strictly essential in the preoperative and postoperative treatment of these cases if recurrences are to be avoided.

Once the gall bladder is infected, its early removal would seem to be indicated, in order to prevent secondary infection to adjacent organs. Judd considers it doubtful whether a gall bladder which has been extensively infected will ever function properly again. It must be remembered, however, that gall bladder disease is a disease of early life, and until we can be more assuredly convinced that this organ can be spared without harm, more conservative procedures are desirable. Early diagnosis is essential in any event. and it is earnestly to be hoped that the evidence secured by means of nonsurgical biliary drainage will soon offer us beyond any doubt more definite and dependable diagnostic data. As with appendicitis and peptic ulcer, the formation of gall stones might better be regarded as a terminal event. By the time they have formed, so much damage has been done to the associated organs that surgical and medical treatment are both heavily handicapped.

Preoperative and Postoperative Management. It may be unqualifiedly stated, I think, that biliary and intestinal stasis are, next to infection, and perhaps even ahead of it in importance, largely responsible in paving the way for the development of chronic gastrointestinal disease. This being the case, the whole subject of the management of these patients boils down to four leading essentials: (1) Eradication of foci of infection, especially in the

teeth, tonsils, sinuses, upper respiratory tract, appendix, gall bladder and colon; (2) elimination of intestinal stasis; (3) elimination of biliary stasis; (4) application of such measures as will improve the general condition of the patient.

The correction of intestinal stasis requires attention to diet and habits, general and abdominal exercises, abdominal supports, etc., none of which will be discussed at this time. I desire to give special emphasis to the value of drainage of the intestinal tract, which is just as essential, when indicated, as is biliary drainage. Transduodenal lavage, using the method of Jutte, also affords considerable relief in those cases of ileal stasis associated with colonic stasis.

By far the most satisfactory method of combating biliary stasis is by nonsurgical drainage. The writer has observed the effects of a large number of therapeutic biliary drainages, and in most instances decided benefit was secured. Lyon, Eggleston, Smithies, Niles, Umber and many others report beneficial results from nonsurgical drainage. According to Moynihan, the recurrence of stones after operation is frequently due to inadequate drainage of bile, that does not permit the escape of grit in the lower intrahepatic ducts and in the hepatic and common ducts. The practical importance of this method of treatment is therefore obvious.

In addition, such general and supportive measures are indicated as will strengthen the bodily resistance. There can be little question that a faulty or poorly balanced diet that is deficient in vitamins and such mineral substances as calcium, iodin and phosphorus must of necessity lead to general devitalization and lessen tissue resistance in the alimentary tract, which affords opportunity for bacterial invasion and subsequent disease. McCarrison's[15] work in this field is of particular interest. He spent nine years among the inhabitants of Himalaya, and performed on an average 400 major operations each year. During this time he was impressed with the infrequency of peptic ulcer, appendicitis and cholecystitis among these people. He attributes the freedom from those affections to their diet, the significant feature of which is the absence of white bread, potatoes, refined cereals, polished rice, sweets made of refined sugar and butter substitutes. McCarrison's suggestion, that one should eat one raw fruit, one uncooked vegetable, two green vegetables and 1 quart of milk daily, with a liberal supply of brown bread, butter, and only enough meat to supply the nutritional needs of the body, is of more than passing interest, and, if adopted, would unquestionably help in the prevention and treatment of alimentary disease. The consequences resulting from inadequate diet have been repeatedly proved by animal experimentation.

As long as one overlooks fundamentals in the management of these patients, and continues to make of them alkali addicts and

tube fiends, just so long one may not expect to reduce the number of operations performed on them, and the recurrence of symptoms after operation. The path of the chronic intestinal invalid is stormy, if not tempestuous; her comforts are meager; her miseries abundant. To our chagrin we not too seldom find that she has improved under the soothing and solicitous ministrations of the science healer or the confidently administered tomfoolery of the cultist. In any case they have secured for their patient a tranquillity of mind and a state of optimism and revived hope that we, either unknowingly or because of our inability, have failed to secure; such an accomplishment is frequently a key to a cure.

A note of caution may wisely be sounded in advising against indiscriminate surgery for chronic gastrointestinal disease. Surgery, however helpful, must in no sense be expected to secure complete relief for the patient. It is far from my intention to cast any shadow of doubt on the splendid and legitimate triumphs of modern abdominal surgery, but we must bear in mind that the performance of any operation that does not cure the patient of the ailment for which it was undertaken must needs bring surgery into disrepute, and arraign our medical profession before a jury of inquisitors of our wisdom.

Summary. Accumulating evidence reveals the fact that operations for chronic appendicitis, peptic ulcer and cholecystitis frequently fail to relieve the patient. The probable explanation of such failures is attempted, in which the etiology, the presence of multiple lesions in the gastrointestinal tract and other associated conditions leading to errors in diagnosis are discussed. Consideration is also given to the preoperative and postoperative management of such patients.

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THE PROPER CLASSIFICATION OF THE CEREBRAL PALSIES OF EARLY LIFE.*

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As long ago as 1890 Dr. Peterson and I published a paper on the cerebral palsies of early life, in which we attempted to bring order out of chaos, and to establish what we thought was a proper clinical and pathologic arrangement of the spastic paralyses of childhood. Considering the relative frequency of these palsies and the serious effect they have on the entire development of the individual, it is strange that they should have held the attention of physicians less than almost any other order of disease, and yet they are responsible for the crippling of many an individual who might otherwise be equal to the average; the same causes which produce these palsies are also responsible for many of the cases of epilepsy and idiocy.

By "proper classification" I mean "proper interpretation" of these conditions from the clinical and pathologic point of view. During the past few decades important contributions have been made by Freud, Batten, Pierce-Clark, Ramsay Hunt and, very recently, by James Collier of London. A number of French and German writers have also been interested in the various subdivisions of the general subject.

The cerebral palsies of early life comprise a great variety of conditions, and any theory which would attempt to attribute all of them to any one cause could not possibly be correct. This is the cardinal difficulty with the attempt made by Collier to hold a primary degeneration of the cerebral neurons responsible for the development of all diplegias. To understand the subject at all, we must realize that this group comprises, clinically, all the diplegias and the paraplegias of early life as well as many odd forms of chorea, athetosis and the socalled choreiform or athetoid paralyses. We must also realize that while the first symptoms appear in the earliest months or years of life, some of them are evidently due to prenatal causes, others to difficulties during labor, while another

* Read before the New York Academy of Medicine, April 16, 1925.

and very important group are the acute or acquired palsies. While a very considerable number of the acquired palsies are hemiplegic in character, not a few are distinctly diplegic and some are paraplegic. All of these forms have certain features in common. The paralysis, whether it be a hemiplegia, a diplegia or a paraplegia, is invariably spastic. With it are associated, contractures and increase of all the deep reflexes in the parts involved; choreic, athetoid and associated movements of the paralyzed parts constitute a very characteristic feature of all these forms. Disturbances of sensation are unimportant. In the acute cases coma and convulsions may mark the onset, and convulsions may be so frequent as to imply a complicating epilepsy. Mental defects of varying degrees are developed in the course of years. The presence of spasticity and the entire absence of changes in the electrical reactions, the relatively slight atrophy of the muscles, help us easily to differentiate between the cerebral and the spinal palsies of early life. I need say little about the distribution of these cerebral palsies, except to note briefly that in a series of 225 cases which Peterson and I recorded, there were 81 right hemiplegias, 75 left hemiplegias, 39 diplegias and 30 paraplegias, and of the total, 134 were males and 91 females.

This general clinical division has been maintained throughout all the discussions, but other forms have been described. Clark has reported a series of cases which he has described as a cerebrocerebellar diplegia of flaccid, atonic type, and Ramsay Hunt has, very properly, segregated a series of cases under the heading of diataxia cerebralis infantilis. This ataxic type of cerebral birth palsies is characterized by "a generalized disturbance of coördination, involving the gait and station, the use of the arms and legs and the muscles subserving the function of speech. The incoordination persists in the recumbent position and has the characteristics of a true ataxia." There is neither paralysis nor spasticity, nor epilepsy nor serious mental defect. There will be little difficulty in accepting Hunt's type, as it will fit in very well with the general conception that clinical types of infantile cerebral palsy will vary in accordance with the distribution of the anatomic lesion. We all know that the hemiplegias are the expression of unilateral brain lesions, that the diplegias, double hemiplegias, can only be due to lesions in both halves of the brain, while the paraplegias may be due either to double brain lesions or, at least, to lesions affecting both pyramidal tracts. If the lesion involves the motor areas of both hemispheres, or the tracts immediately connected with them, we can readily understand the development of double hemiplegia. If the cerebellum be involved we may possibly be able to account for the types that Clark has described. Batten, by the way, has described a pure cerebellar type of diplegia. Foerster, in 1904, recorded an atonic astasic type, which he ascribed

to extensive lobar sclerosis of the frontal region, and Hunt believes, without definite anatomic evidence, as he himself states, that his type may be due to injury to the fetal head at birth, producing rupture or thrombosis of the cerebral veins with limitation of the lesions to the cortex of the parietal lobes. In this he approaches Gowers' concept of the importance of the meningeal veins in all these disorders. Hunt considers the diataxic form to be the sensory equivalent of cerebral diplegia and argues very correctly that the parietal lobe is the great receptive center for the registration of sensory stimuli. I hope that through some fortunate circumstance Hunt may be able to prove his theory to be entirely correct. It is plausible and entirely acceptable as a theory.

On clinical grounds there can be no objection to the establishment of a large number of types. Some confusion, however, has been produced by the fact that many authors have spoken of Little's disease as though it were a distinct clinical entity. The confusion was so great many years ago that, among others, I was led to ask, in 1897, "What is Little's disease? shall we retain the name?"

I stated that Little's disease is "whatever an author pleases to make it." Some of the facts may be rehearsed briefly: In 1862 Little published a very important paper on the influence of abnormal parturition, premature birth and asphyxia neonatorum, in which he showed that the spastic rigidities and the spastic palsies appearing early in life were due to protracted labor and premature delivery. German and French authors who took hold of this conception applied the term "Little's disease" to all early spastic rigidities and palsies, and this same custom has largely prevailed up to the present time, so that it has been the practice among many writers to speak of all congenital diplegias and paraplegias as Little's disease and, somewhat illogically, they have held that the etiologic factor which Little stipulated for the cases which he recorded was the universal cause of all these early spastic diplegias and paraplegias.

Used in this way, the name is an entire misnomer, for many reasons. First of all, we now definitely know that not all of the cerebral diplegias and paraplegias are due to difficulties at birth, or to premature delivery, and we also know that difficulties during labor produce hemiplegias as well as diplegias or paraplegias. If the name is to be used at all, it should be restricted entirely to forms of spastic paralysis, whether they be unilateral or bilateral, that can be definitely ascribed to difficulties during labor or to premature birth.

For all practical purposes it will be well to pay less attention to the exact form of the paralysis so long as we know it to be definitely cerebral and not spinal, and to group the various cases according to the time of onset and to the morbid lesions that have been definitely ascertained to be the prime cause of one or the other

forms of paralysis. Simple as this question of the morbid lesions would appear to be, the one great obstacle to a clear understanding of the subject is that in a large number of cases the lesions found represent terminal states, while every vestige of the primary pathologic process has disappeared. Another difficulty met with is that even though the first signs of paralysis may be evident several months after birth, or immediately at birth, such paralysis may be the expression of morbid processes beginning during the intrauterine period, or of imperfect development of the motor system.

The general classification which I presented in 1895 has met with the approval of many writers. Recent studies call for some modification.

CLASSIFICATION OF INFANTILE CEREBRAL PALSIES.

Groups.	Clinical forms in order of frequency.	Morbid lesion.
I. Paralyses of intrauterine onset	Diplegia, paraplegia, hemiplegia	Large cerebral defects (porencephaly); defective development of pyramidal tracts; agenesis corticalis (highest nerve elements involved); polioencephalitis (?); primary neuronal degeneration.
II. Birth palsies	Diplegia, paraplegia, hemiplegia, diataxia, cerebellar form	Meningeal hemorrhage, rarely intracerebral hemorrhage. Later conditions: Meningoencephalitis chronica; lobar sclerosis and cysts; partial atrophies.
III. Acute (acquired) palsies	Hemiplegia, paraplegia, diplegia, choreic and athetoid disorders (unilateral and bilateral)	Hemorrhage (meningeal and rarely intracerebral); thrombosis (from syphilitic endarteritis and in marantic conditions); embolism. Later conditions: Atrophy; cysts and sclerosis (diffuse and lobar); meningitis chronica; acute encephalitis (cortical and striatal); polioencephalitis acuta (Strümpell).

In the first group, the paralysis of intrauterine onset, we know that the paralysis may be due to large cerebral defects known as porencephaly, that there may be defective development of the pyramidal tracts, that in some cases there may be an *agenesis cerebralis* or a defective development of the highest nerve elements of the entire central nervous system. In some there may be, accepting Collier's designation, a primary neuronal degeneration. The occurrence of an intrauterine infectious encephalitis has been looked for, but not proved. Clinically, this group includes the cases of diplegia or paraplegia which may or may not be associated with choreic and athetoid movements. Some, in the course of years, develop marked mental defects; others, again, go through life with a fair mentality but with markedly disturbed motility.

There is the closest possible resemblance, clinically, between Groups I and II. The palsies of Group II are due to difficulties

during labor, to prolonged labor or instrumental delivery. First-born children are especially prone to these affections. The primary cause is a meningeal hemorrhage, rarely an intracerebral hemorrhage. The terminal conditions may be a chronic meningoencephalitis or a lobar sclerosis. In some instances cysts and partial atrophies are found.

I have said above that hemiplegias are sometimes due to difficulties during labor, so that there might be hemiplegias that could be construed as distinct birth palsies; but the diplegias and paraplegias have stood in the minds of many as the clinical representatives of true birth palsies or of paralysis due to intrauterine affections, or to developmental defects, and in this way much confusion has been created. This confusion has been increased by the recent article of James Collier who, in a Presidential address, delivered before the Neurologic Section of the Royal Society of Medicine, in October, 1923, has endeavored to maintain the proposition that all cerebral diplegias are due to disturbances in development, and has gone especially out of his way to show, so far as the group of birth palsies is concerned, that we have been misled all these years in attributing great importance to the communication of Dr. Sarah McNutt, in 1885, in which she showed that diffuse meningeal hemorrhage over one or both hemispheres at the time of birth is responsible for some of the cases of double infantile spastic hemiplegias.* I have gone over the original paper of Dr. McNutt on double infantile spastic hemiplegia, and can find no fault with her conclusions. In her case the child was the sixth in its family, and was delivered with instruments. Convulsions occurred during the first nine days of its life, with but short intermissions (very strong evidence of an irritative process). There was a spastic diplegia, cross-legged position and repeated epileptic seizures. Death from pneumonia occurred at the age of two and a half years. Amidon and W. H. Welch are sponsors for the pathologic findings, which show clearly a double well-localized active process leading to "atrophy of the paracentral lobule of the central convolution," and so forth, just where hemorrhage from application of forceps might have been expected. Welch's report disproves Collier's theory of a primary degenerative affair. Welch's diagnosis reads: "Sclerosis of the greater part of the motor cortical area in both hemispheres with secondary descending degeneration of the pyramidal tracts."

Collier insists that the morbid process was begun long before birth; he infers this from the primitive nature of the arrangement of the convolutions and from the condition of the pyramidal tracts.

* If proof were needed of the frequency of meningeal hemorrhage at birth, we might add on the authority of Peterson that Litzmann examined 161 stillborn children, finding in them 35 cases of meningeal hemorrhage; that Parrot in 34 autopsies on the newborn found 5 with blood in the arachnoid cavity and 26 with hemorrhage into the subarachnoid space.

Collier's argument is not at all convincing and, while it may not be correct to ascribe all cases of diplegia or hemiplegia appearing shortly after birth to natal hemorrhage, the evidence that such hemorrhages do occur is almost overwhelming, and there is no reason in the world to discard such evidence in favor of a theory which may be ingenious but not satisfying.

In seeking further proof of his theory, Collier refers to the fact that in amaurotic family idiocy there is a primary neuronic degeneration. He says that this origin has always been accepted, and it is his contention that this disease should be included among the diplegias. He also goes on to say that the disease is characterized by marked paralysis, sometimes there is optic defect and "sometimes no familial or racial incidence can be traced." The argument is faulty, and the facts are not stated carefully. The paralysis in many of these cases is only incidental, as I pointed out years ago. There is not a single case without optic defect, and if there ever was a disease in which there was distinct familial or racial incidence, it is this form of family affection; yet Collier bases his argument largely upon the primary neuronic degeneration occurring in this special form, which is not a typical diplegia. That many of the diplegias are related to hereditary and family disease I have at various times conceded, but there is no reason to ascribe all of these diplegias to this one cause. It is interesting in this connection to take note of van Gehuchten's theory, that the pyramidal tract reaches the medulla at the end of the seventh month of fetal life, and that this failure of development of the pyramidal tract would cause rigidity of the trunk and of all four limbs. In cases of premature birth at the end of the eighth month it has reached the dorsal region, and therefore premature birth at this time would cause rigidity of the lower limbs only. After birth the arrested growth is amended, and for this reason some of these cases tend to improve and sometimes to recover. The theory of primary neuronal degeneration may suffice as an explanation for some of the cases that we may, roughly speaking, ascribe to defective development of the central nervous system, but it can surely not be held to be the chief cause of all the cerebral diplegias.

Let me review, briefly, a few significant clinical facts. The palsies due to intrauterine disease or to arrested development, and those due to traumatism during labor give a distinct history of early onset of all the symptoms. Bilateral palsies are more common than in the acute cases, but the paralysis is not necessarily complete. At times it is a simple paresis; at other times rigidities and contractures are more prominent than are the palsies. Little made a sharp distinction between rigidities and palsies. In this he has been followed by some continental writers, but Freud, Peterson, Sachs and other American writers have maintained that rigidity, contracture, choreic or athetoid movements, paresis, uni-

lateral or bilateral, constitute a graduated series of disturbances due to cerebral lesions in children. Each or any one of these clinical manifestations may be present in a given case and may vary according to the site and intensity of the lesion. It is not uncommon to find that in cases of diplegia there may be paralysis in the lower extremities and athetosis in one or both upper extremities. Double athetosis is a condition closely analogous to double hemiplegia with less paralysis, however, than in the majority of other spastic palsies. The studies of encephalitis have convinced us that the choreic and athetoid movements are more apt to be present with lesions of the basal ganglia than in those involving chiefly the pyramidal tracts from the cortex downward. In other words, that they are apt to be due to extrapyramidal disease. Freud, who was one of the best students of this entire subject, found it necessary on purely clinical grounds to subdivide the diplegias into four groups: (1) Universal spastic rigidity; (2) paraplegic rigidity; (3) bilateral hemiplegia; (4) bilateral chorea and bilateral athetosis. I have no doubt that we shall be able soon to give the exact anatomic basis for these various clinical subdivisions. It is worth noting that Charcot, Marie, Déjerine and others insisted that congenital spastic paraplegia may be a spinal affection and due to defective development of the pyramidal tract. This may be true, but the high percentage of idiocy among children with congenital paraplegia leads to the inevitable conclusion that disease of the pyramidal tract alone cannot be held responsible for the entire group of symptoms observed in so many of these cases.

Many interesting questions arise in connection with the third group of cases—the acute (or acquired) cerebral palsies of children. Why do children develop these palsies? What are the points of resemblance and the points of difference between these acute palsies of early life and the typical apoplexies of the senile and presenile period?

There can be no doubt that hemorrhage, embolism and thrombosis, the conditions which give rise to the vast majority of apoplexies in the adult, are important factors in the causation of the acute cerebral palsies of children. In studies made many years ago by Osler, Peterson and myself it was found that in one series of 78 cases there was definite evidence of hemorrhage in 23, of embolism in 7 and of thrombosis in 5 cases. In 42 other cases terminal conditions were reported and these were more or less useless in helping us to ascertain the primary lesion. In Osler's series of 90 brains which he examined he reported a vascular lesion in only 16, of which 7 were due to hemorrhage and 9 to embolism. But, of course, a very large number of cystic conditions that were included in the Osler series may have been originally due to hemorrhage or embolism. The causes which lead to embolism and thrombosis in children may be inferred from the conditions in the adult pre-

disposing to these same vascular accidents. Some writers insist upon a greater frequency of embolism, others believe that hemorrhage is more frequent in children, while Gowers stood alone in maintaining that thrombosis of the superficial veins is a noteworthy initial lesion. Hunt has joined him in this. With regard to the occurrence of hemorrhage in children, it is fair to inquire what morbid condition of the bloodvessels in children would rank with the arteriosclerotic changes and the miliary aneurysms of the adult.

I gave a great deal of thought to this matter many years ago, and was relieved to find that von Recklinghausen, in his masterly monograph, stated that fatty degeneration of the bloodvessels in children is frequent, and may be accepted as a partial explanation of the occurrence of hemorrhages in the infantile and youthful brain. Steiner had expressed a similar view. I was also puzzled to discover why in the adult the majority of hemorrhages occur in the vicinity of the internal capsule, whereas in the child they are more apt to occur in or near the cortex. I had to fall back upon the theory that the greater delicacy of the superficial bloodvessels of the pia and of the cortex accounted for the more frequent cortical and meningeal hemorrhages in children. But I was also aware, thirty years ago, that intracerebral hemorrhages, embolism and thrombosis occur occasionally in children, exactly as they do in the adult, and that they give rise to clinical symptoms in no wise different from those of ordinary apoplexy. Much of this speculation was superfluous, since it is fairly well established at the present day that infantile encephalitis is much more common than it was supposed to be, and I have no doubt that some of the hemorrhages reported by former authors were part of an inflammatory process. In former years I could not accept Strümpell's well-known theory, that the acute hemiplegias of children were due to a polioencephalitis, which he thought akin to the poliomyelitic infection. Strümpell had no anatomic evidence to offer at that time, and his argument was based largely upon a few cases reported by Moebius and others, that cases of infantile spinal paralysis and infantile cerebral paralysis had occurred in several children of one and the same family. Strümpell's contention was no doubt extreme, but we have every reason to believe that he was correct in surmising the infectious encephalitic origin of many of these cases. Relying upon the resemblance to adult apoplexy, and in former years believing that adult apoplexy was invariably due to a vascular lesion, I depended largely upon a series of cases like one that I had occasion to observe in a boy, aged two and a half years, who after a simple attack of tonsillitis developed right hemiplegia with motor aphasia coming on without coma and without convulsions. The aphasia disappeared after two days and the hemiplegia also improved. Within a few weeks the young boy was entirely well

and scarcely retained a trace of the apoplectic condition. There was no history of syphilis in this case, and the entire development and retrogression of the symptoms reminded one of an adult apoplexy. I felt that the possibility of thrombosis could not be excluded, but whether hemorrhage or thrombosis, there could be no doubt that the lesion was intracerebral and not cortical, as in the majority of cases in children. Curiously enough, Déjerine, in 1891, reported 3 cases in which there were distinct hemorrhagic lesions in the vicinity of the larger ganglia, exactly where we nowadays find the chief sites of the encephalitic process.

Carrying the argument a little farther, let me state that in the recent epidemic of lethargic encephalitis we have had occasion to observe what appeared to be true apoplexies in the adult. The case of a well-known man in this city, whom I had the opportunity of observing in company with Dr. Dana, was particularly instructive. The patient presented for a number of days the typical clinical picture of a hemiplegia due, supposedly, to thrombosis. The development of partial paralytic symptoms on the opposite side of the body with dysarthria and some occular palsies proved, together with other signs, that in the adult acute hemiplegia may be the expression of an encephalitic process. There is less reason therefore than there formerly was to draw a sharp line of demarcation between the apoplexies of childhood and the apoplexies of adult life. Both in the adult and in the child we must now conclude that vascular lesions may be a frequent cause but not the sole cause, and in childhood I am now convinced that an encephalitic process of any of the well-known infectious types, lethargic, influenzal or what not, may be a frequent cause of these acute cerebral conditions.

I have not hitherto alluded to one question of great practical interest, and that is, whether or not convulsions *per se* produced paralysis in children or whether both the convulsions and the paralysis are due to the same cause. The truth, in all probability, lies midway between these extremes. In the distinctly infectious forms we may assume that the infectious process is responsible both for the paralysis and for the convulsions; but when a child has had a series of convulsions at shorter or longer intervals, and hemiplegia appears immediately following a severe convulsion, the venous stasis occurring during the acme of the convulsions may be held responsible for the development of the hemiplegia, and that this is not a mere theory but an anatomic fact has been definitely established by postmortem examinations of my own.

If we take up the points of difference and the points of resemblance between the palsies observed in children and in the adult we have still further reason to stress the possible and probable encephalitic origin of many of these cases. The startling difference noted in former years was the occurrence of choreic and

athetoid movements in association with the cerebral palsies of children, whereas in the adult such complicating disturbances of motility are relatively rare. Here again the studies of encephalitis have revealed the very striking fact that tremors, choreic, athetoid and myoclonic movements, are extremely common in association with the paralysis due to encephalitic conditions and the physiologic and anatomic studies of Hunt, Jakob, Vogt and many others have definitely shown that these unusual disturbances of motility, of posture and gait, are distinctly due to lesions of the extrapyramidal system.

Involvement of the neostriatum—the putamen—is held responsible for the development of double athetosis, a combination of choreic and athetoid movements. Lesion of the paleostriatum—the globus pallidus—is characterized by paralysis of automatic associated movements, by muscular rigidity and tremor: The clinical signs of paralysis agitans. When the entire striatal system is involved, as in Wilson's disease, we get a combination of rigidity and tremor with tonic and clonic spasms. It can easily be seen that the disturbance of motility associated with these early palsies may be ascribed to involvement of one or both striatal systems.

The corpus striatum stands in close relationship with the optic thalamus, and through it with the peripheral sensory apparatus, with the cortex cerebri and with the cerebellum.

I do not wish to enter into the many interesting details that have been developed in connection with the study of extrapyramidal diseases,* but must utter at least one word of caution, and that is, that it will not be safe to consider the globus pallidus or the putamen, or the striatal system as a whole, the sole site of the infantile cerebral palsies. The frequent association of idiocy, of imbecility, of epilepsy and the more frequent occurrence of convulsions in the cerebral palsies of children compel the conviction that the cortex must not be slighted or overlooked. Very careful examination of all parts of the brain will be needed to establish the complete pathologic record of these acute infantile cerebral palsies. If we accept the encephalitic origin for many of these acute spastic palsies we shall have no difficulty in explaining the occurrence of the unilateral as well as bilateral symptoms, and we need not be astonished every now and then to find diplegias as well as hemiplegias to be the expression of an acute or acquired cerebral lesion in childhood. Strümpell, who was right in so many things, was definitely wrong in maintaining that *hemiplegia* in children was synonymous with the acute infantile cerebral palsy. If his term, polioencephalitis, is to stand at all it must apply to the diplegic as well as to the hemiplegic forms.

* The subject has been discussed fully by Hunt, Jakob, Haberman and others.

Conclusion. In conclusion, let me emphasize the general proposition that, in attempting to classify or to interpret the cerebral palsies of children, the exact form of the paralysis is the unimportant factor. It is much more important to determine, whatever the form may be, whether the palsies are due to a morbid process that had its beginnings in the prenatal period or at the very time of birth, or whether they were acquired later in life as the expression of vascular accident, or as the result of an infectious encephalitis.

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INCIPIENT GENERAL PARALYSIS.

A Study of the Earliest Symptoms Presented by Seventy-four Cases.

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The purpose of the study of which this paper is a brief report has been to determine as accurately as possible the nature of the earliest symptoms which made their appearance in a series of 74 male patients who were committed to the Manhattan State Hospital on account of fully-developed general paralysis during the past two years, and thereafter studied on the service of the New York Psychiatric Institute. The opportunity to investigate anamnestically the earliest departure from their normal state of health which

these patients manifested was enhanced by the fact that in a majority of instances cases were selected with the intelligence and observational ability of the informant (usually the wife of the patient) in mind. Thus, it is felt, has been obtained a fairly faithful picture of the patient at a stage in the evolution of his disease when he presented, at least from a symptomatic standpoint, nothing characteristic of general paralysis, as later seen and as commonly thought of, or indeed of neurosyphilis of whatever type; at a time when the patient, in other words, had advanced perhaps a single step beyond the strictly asymptomatic stage of the neurosyphilis which had been present in latent form, according to our present knowledge, almost from the time of his initial infection. If, then, the occurrence of certain symptoms can be shown to carry with it the possibility that, if not otherwise to be accounted for, they may have their origin in neurosyphilis and perhaps even in the more malignant form of that condition known as general paralysis, this fact will suggest the necessity for examination of the spinal fluid in numerous instances in which this procedure is not now carried out. For, obviously, the crucial factor in the diagnosis of neurosyphilis, and *a fortiori* of general paralysis, lies in the examination of the spinal fluid; and the essential practical problem involved consists in the recognition of the indications for such examination. Since the actual, if less immediate purpose of this study, is to indicate in a very partial way certain means whereby an earlier diagnosis of general paralysis may be achieved, we may take the liberty of preceding the discussion of our case material by a brief reference to the indications for spinal-fluid examination, without which a diagnosis of neurosyphilis is not seldom wellnigh impossible, and of general paralysis at an early stage of its evolution practically out of the question.

There are three phenomena, the occurrence of any one or more of which should raise the question of the desirability of lumbar puncture, while its omission in the presence of any two of these phenomena places the responsibility upon the physician who rejects the need for examination of the spinal fluid under these circumstances. These three findings are as follows:

1. A positive Wassermann reaction in the blood might not be considered as in itself an indication for lumbar puncture; yet it is the practice in the best clinics to perform a lumbar puncture upon every syphilitic prior to his discharge at the time the Wassermann reaction in the blood has been rendered negative. For every syphilitic is a possible neurosyphilitic; while it is also to be remembered that a not inconsiderable proportion of neurosyphilitics have a persistently negative Wassermann reaction in the blood serum. All "Wassermann-fast" patients are not neurosyphilitic; yet in many cases the persistence of a positive Wassermann in spite of protracted treatment is due to the presence of neurosyphilis. It is perhaps

of some interest, in suggesting, moreover, that these remarks are not wholly superfluous, that in an appreciable proportion of the patients in our series who early consulted a physician a positive Wassermann reaction was found to be present in the blood. Almost without exception, however, no effort was made, in spite of this fact and of the complaint of definite "nervous" symptoms as well, to establish the presence or absence of neurosyphilis. These same patients accordingly received antisyphilitic treatment of a purely routine character such as might conceivably have had a favorable influence upon neurosyphilis of the meningovascular and hence relatively "benign" type, but could not possibly be effective against the parenchymatous or "malignant" form of the disease from which these particular patients, as the event only too clearly proved, were beginning to suffer.

2. With or without a positive Wassermann in the blood, certain physical signs are, when present, distinctly suggestive, and sometimes practically proof positive, of the presence of neurosyphilis. Pupils which are unequal or irregular or which react to light with impaired briskness or degree of excursion are ground for strong suspicion, while in the true Argyll-Robertson pupil we have that medical *rara avis*, a pathognomonic sign—for a pupillary reaction of this latter type is practically pathognomonic of syphilitic involvement of the central nervous system. Absence or definite inequality of the knee jerks (or of the ankle jerks without absence of the knee jerks) is likewise a sign of highly suggestive value. On the other hand, the absence of any or all of these signs does not exclude the presence of neurosyphilis; nor is it possible, for obvious reasons, to state with exactitude what proportion of early neurosyphilitics do or do not exhibit them. When definitely present, they assuredly call for examination of the spinal fluid.

3. Certain symptoms, both physical and mental, of very varied character and in themselves relatively or absolutely undistinctive in their nature, occur with some prominence as the earliest manifestations of clinical neurosyphilis in many cases, and are at least equally characteristic of the earliest onset of general paralysis. In the presence of either of the two findings already mentioned, even the least distinctive of these symptoms may take on a significance which they could hardly otherwise possess. But with or without the coexistence of a positive Wassermann reaction in the blood or of suspicious neurologic signs, the occurrence of such symptoms, when they cannot be adequately accounted for on other grounds, should raise the question of their neurosyphilitic etiology and accordingly should make examination of the spinal fluid most desirable. Indeed, it may be laid down as a rule that the presence of any nervous or mental symptom whatever, if that symptom cannot be explained beyond reasonable doubt on some other basis, is cause for making an examination of the spinal fluid; such is the pro-

tean character of neurosyphilis and of its subspecies, general paralysis.

So far as our immediate topic, the early diagnosis of general paralysis, is concerned, the recent words of Stokes with regard to early tabes are equally in point: "The attention of the profession should therefore be focussed consistently on the subjective symptomatology, and when any of its leading points are developed in a case history, a quick search for early signs should be made as a routine," in order that, as he goes on to say, lightning pains shall no longer pass as "rheumatism" or "neuritis" in the face of absent pupillary light reflexes or knee jerks, "slow" bladders be called stricture, or gastric crises be operated on as gallbladder attacks. And while it is perhaps true that the analogous leading points in the diagnosis of early general paralysis tend from their mental rather than physical character to be more indefinite and more equivocal than is often the case in tabes, it is at least equally desirable that "nervousness" shall not demand simply a "rest cure" in the face of the physical signs just mentioned, nor a definite change in the patient's personality or emotional status be set down exclusively to worry or "nervous strain." This, then, is the justification for presenting, even though briefly, the results of our inquiry into the earliest symptoms of which 74 patients complained, who, nine months to even four years later, developed outspoken general paralysis, and in whom these early symptoms, whether or not accompanied by physical signs or a positive Wassermann in the blood, were in almost every case disregarded or misinterpreted. This error resulted, (1) because their possible significance was not appreciated, and (2) because their meaning was not further probed by a search for suspicious neurologic signs or confirmed by examination of the spinal fluid. Indeed, it might be claimed with some reasonableness that the early recognition of general paralysis has lately assumed an increased importance in view of the fact that we now have, in tryparsamide and in malaria, a therapy of such increased effectiveness that a striking degree of clinical remission with restoration of previous efficiency can be obtained in no small proportion of patients treated by these measures, provided only that they are treated early enough in the disease.

By far the commonest early symptom found in the patients in this series seems to be that which may be somewhat loosely termed *irritability*. It is usually stated that this manifestation is in sharp contrast to the patient's ordinary disposition, but there are, of course, instances in which the change represents an exaggeration, perhaps gradual but sooner or later definite, of a normal tendency to irritability on the patient's part. Or his emotional instability may take a somewhat different direction and manifest itself as a too ready, even if evanescent, emotional response of a sorrowful, depressive, or even tearful character. (It is perhaps interesting

that the opposite tendency to morbid elation or euphoria, which is often thought of as especially characteristic of general paralysis, does not once appear, at least in the present series, among the very earliest symptoms of the disease.) To these various manifestations of emotional instability, differing somewhat in kind and very distinctly in degree, the informant is prone to refer simply as "nervousness." This symptom was among the first to be noted in 42 of our 74 cases; in 18 it constituted the earliest departure from the normal observed by the informant; in 12 cases it followed some other symptom by a period of one to six months; in the remaining cases it was the third change noted in the patient, but in most of these its appearance was more or less simultaneous with that of the second. When this alteration in the personality of the patient was the first deviation from the normal to appear, it usually antedated the onset of frank mental symptoms by at least six months and not infrequently by a year, a year and a half, or even longer. In 1 case, indeed, a very intelligent informant was positive that a change in the patient of this description was observable nearly five years before the outbreak of acute psychotic symptoms. Irritability is, of course, far from being a distinctive manifestation. It is a characteristic of organic disease of the brain, is sometimes seen in diabetes and in nephritis, and may indeed be a reaction to any form of ill health. It is often a "functional" symptom and may form part of the clinical picture of a psychoneurosis. The fact that it occurs as one of the earliest changes in more than half of the present series of cases, however, suggests that its occurrence in a patient makes it desirable to exclude general paralysis as its possible cause.

Psychologically somewhat allied to this symptom, perhaps, is the condition referred to by the informants as restlessness. The patient is described as "nervous," "fidgety;" he is no longer content, as formerly, to remain at home after dinner, for example; he wants to be somewhere other than where he is, or to do something other than what he is doing. This is, perhaps, a more subtle alteration in the patient than even the milder degrees of irritability or of emotional instability, and it is possibly on this account that it appears in only six of our histories, and these among the most intelligent in the series. It is not unlikely that it accompanied or preceded the irritability in a number of the patients exhibiting the latter, and in fact the two symptoms are given as coexistent in the patient just referred to, in whom these antedated the outbreak of a definite psychosis by nearly five years. It is of interest, moreover, that the onset of this socalled restlessness preceded the appearance of frank mental symptoms by a considerable period; by a year or more in 2 of the cases, and by more than two years in the others.

The second most common of the earliest changes observed in this series might be considered the exact opposite of the preceding. It is

a symptom difficult to label with a single word, the term "quiet" being that which is most often spontaneously applied by the informant. The patient is described as gradually but noticeably becoming less active than is his ordinary habit; he becomes less communicative and may sometimes gradually lose almost all spontaneity of utterance; he often appears preoccupied, listless or apathetic; he wants to be let alone and is averse to the company of others, especially strangers, often leaving the room upon the advent of visitors; he loses interest in some of the things which formerly entertained him. It is a symptom that appears to correspond to some extent to that mental disturbance found as an occasional accompaniment of chronic epidemic encephalitis which has been termed by Naville as bradyphrenia and which in his description is characterized by "a diminution of voluntary attention, of spontaneous interest, of initiative, of the capacity for effort and for work." This change, in one guise or another, is described as among the earliest noted in 28 cases—the first alteration observed in the patient in 12 cases, and the second in 10. Although seeming on the face of it to represent a deterioration of a rather radical character, in these cases this symptom was usually first noted at least nine months before the onset of a frank psychosis, and in 2 cases was present for four and four and three-quarters years, respectively, prior to commitment.

Closely following in numerical importance this reduction of interest, this seclusive or "bradyphrenic" type of reaction, is *loss of weight.* Although there is evidence that a considerable proportion of these patients lost weight at some time during the evolution of their disease, only those cases are here included in which loss of weight was mentioned by the informant, nearly always spontaneously, as being an early and often rather striking manifestation. Of such cases there are 22 in this series. In 13 of these, loss of weight was the very earliest change noticed in the patient; in 9 it was preceded, often by a rather brief interval, by one other symptom; in no case was it preceded by two other symptoms. Indeed it is likely that some of the patients in this second group really belong in the first; for the onset of loss of weight is obviously difficult or impossible to date within weeks or even months, since it would usually not come to notice before it had amounted to at least 5 or 10 pounds, depending somewhat on the customary weight of the patient. The interval elapsing between the actual onset of loss of weight and the outbreak of frank mental symptoms is probably therefore in some cases an understatement; but it is noteworthy that this interval was never less than four to six months and was usually a year or longer, being at least two years in 1 case, more than three years in 3 cases, and nearly five years in 1 case. The amount of weight lost and the rapidity with which the loss took place and whether this marked the earlier or later period

of the evolution of the disease naturally varied widely in these patients. A loss of 10 or 15 pounds, often at the very outset, was almost invariable, since this would usually be nearly the smallest amount of loss discernible by the observer; a loss of some 25 pounds, took place within the first six months or so in several cases; and 3 patients lost a total of 35 pounds in weight, 2 of these within a year of onset. So far as this particular series is concerned, loss of weight appears, therefore, to assume some importance among the earliest symptoms of general paralysis because of its relative definiteness as a symptom, its early appearance and sometimes rather conspicuous character in an appreciable proportion of cases, and the fact that early and especially fairly well-marked loss of weight characterizes but few diseases—among which diabetes, hyperthyroidism and tuberculosis come most readily to mind.

Forgetfulness, a practically invariable characteristic of fully developed general paralysis, is mentioned as one of the earliest manifestations of the disease in only 15 cases, in but 5 of which it was believed by the informant to constitute the earliest abnormality present and in 7 the second to appear. In 1 case—and here the history was particularly detailed and complete—a mild degree of forgetfulness was noted by the patient's wife three years before the onset of acute mental symptoms. It seems probable, indeed, that this is a symptom which would for some time escape the notice even of intimates, although the patient himself might often be aware of its presence. Forgetfulness as a symptom has at all events the distinction, not shared by the three symptoms already mentioned, that its definite appearance de novo would make one think principally of either cerebral arteriosclerosis, on the one hand, or of cerebral syphilis or general paralysis, on the other.

Another symptom characteristic of organic brain disease, and occurring in this series as one of the earliest features of general paralysis in 15 cases, is an increased *tendency to sleep.* Even when relatively mild, such a tendency appears to come rather quickly to the attention of the patient's intimates. An analogy is seen in the pathologic sleep of many cases of epidemic encephalitis and in fact of other intracranial conditions such as brain tumor, and one is likewise reminded of the daytime dozing of the arteriosclerotic and the senile. In 8 of these 15 cases this symptom was the earliest to appear, according to the informants, but in 4 of these its appearance was considered to be essentially simultaneous with that of at least one other symptom; in 6 cases it was definitely the second abnormality in chronologic order. While the increased tendency to sleep made its appearance in most cases within but a few months before the outbreak of a frank psychosis, in 3 cases it was present for at least a year prior to that event.

The opposite manifestation—*insomnia*—was noted as an early phenomenon in only 9 cases, and in but 2 of these was it given as

the first symptom to appear, while in only 1 patient did it antedate the appearance of frank mental symptoms by any considerable period. In any event the wholly undistinctive character of insomnia as a symptom is self-evident.

Speech defect is, of course, characteristic of many cases of fully developed general paralysis, but it may also occur as one of the earliest symptoms. It occupies such a position in 11 cases in this series. It was the very first symptom noted in 5 patients, and in all of these it appeared some considerable time before the onset of definite psychotic symptoms—seven months in 1 case, a year or more in 3 cases, and five years and ten months in 1 case, while in a sixth patient it appeared, though not as the earliest symptom, a year and a half before the acute onset of his psychosis. In 2 patients the condition was of sudden onset. In several patients speech defect varied strikingly in intensity from time to time.

Defective judgment is a phenomenon also commonly associated with fully-developed general paralysis, being then usually so gross as to play a part in the most ordinary matters. But the question of early slight deviation from the individual's normal status in this respect is a subtle one, and such deviation may be as difficult of detection as judgment itself is difficult of measurement or definition. Few of our patients were in positions of responsibility such as to make lapses in this direction very apparent to the informant, or at least only after an interval of cumulative effect. Even when the informant can adduce evidence of this sort, it often remains something of a question whether the instance specified represents an early indication of the disease which subsequently develops or whether it is possibly something that might have occurred in any case and has only been made conspicuous by the later turn of medical events. For, obviously, it is by no means always possible to weigh the circumstances accurately enough to know whether a faulty investment or an ill-advised change in business, for example, was in fact an actual sign of the disease that was to develop a year or more later. At all events, there are but 7 patients in this series in whom judgment defect ranks as the earliest manifestation of mental disorder. In 3 of these the defect seems nevertheless to have been of the grosser order, an increasingly obvious mismanagement of their business which antedated other symptoms by a few months only. In 3 the situation was more difficult to estimate, the defective judgment manifesting itself four, six and nine months, respectively, before the appearance of any other symptom. In the seventh case it was learned from the patient himself, after he had achieved a very complete remission following malaria treatment, that nearly a year and a half prior to the onset of other symptoms, he had diverted funds of his in a way that to him was clear evidence, seen in retrospect, of mental disorder.

The remaining early symptoms are of a miscellaneous character,

represented each by a few patients only. Unusual *fatiguability* was early remarked in 7 patients; it was the first symptom to appear in 5 cases and the second in 1. In 1 patient it preceded any other symptom by six months, the appearance of frank mental symptoms by a year and one-quarter, and commitment by twenty-three months. Under this heading might be mentioned the early complaint of 2 or 3 patients of their awareness that there was something indefinable the matter with them, without their being able to say what it was—a feeling that they were somehow "not themselves." *Digestive disturbance* was the initial abnormality in 7 cases. In 1 of these it began three years before the actual mental breakdown and four years before commitment; in 2 cases it antedated mental symptoms by at least a year. In most instances the disturbance seems to have consisted of intermittent epigastric distress with little or no relation to meals; in 2 patients there was vomiting after nearly every meal, which passed off, however, in the course of three or four months. In 6 patients *impairment of vision* was mentioned as the very earliest evidence of disease. In 3 of these the condition rapidly advanced to optic atrophy and complete blindness, the onset of visual impairment antedating the appearance of definite mental symptoms by two, three, and six years, respectively. In a fourth case optic atrophy was unilateral. *Headache,* usually occipital, was prominent among early symptoms in only 4 cases; but it was the very first symptom to appear in only 1 patient. In 4 patients, *tremor,* usually of the hands, was noted among the earliest symptoms, but it was always preceded by at least one or two other symptoms. Three patients early manifested a *slowing in their movements;* it was in each case the second abnormality to appear, according to the informants, but followed the first at a brief interval of a month or two. A not uncommon manifestation of later general paralysis, it is perhaps the physical component of the bradyphrenic reaction which is frequently characteristic of even the earlier stages of the disease, while it also suggests the purely motor sluggishness seen in the Parkinsonism of chronic epidemic encephalitis. Of 4 patients it was stated that vague *rheumatoid pains*—in the shoulders, the arms, or the legs—appeared very early. In 3 cases they represented the very earliest symptom (appearing more or less simultaneously with digestive disturbance, however, in 2 of these), while in the fourth case this symptom, although the third to appear, did so nearly four years before the commitment of the patient was necessary. In 2 cases some unsteadiness of gait accompanied this symptom. In all 4 cases these pains disappeared after a few months. In 1 additional case it was stated that definite *numbness,* first of the right foot and presently of the right hand, made its appearance three and a half years before the onset of any mental symptoms whatever.

Fig. 1 presents in graphic form the relative incidence of these early symptoms in the 74 cases. It has been thought of some interest to distinguish between the frequency with which a given symptom appeared among the earliest abnormal manifestations, and the frequency with which it presented itself as the very earliest departure from the normal to occur.

Of the foregoing symptoms, which in this series have been the earliest to appear in cases of incipient general paralysis, it is clear that only three are in themselves at all suggestive of that disease, or of neurosyphilis of any type. These are speech defect, memory

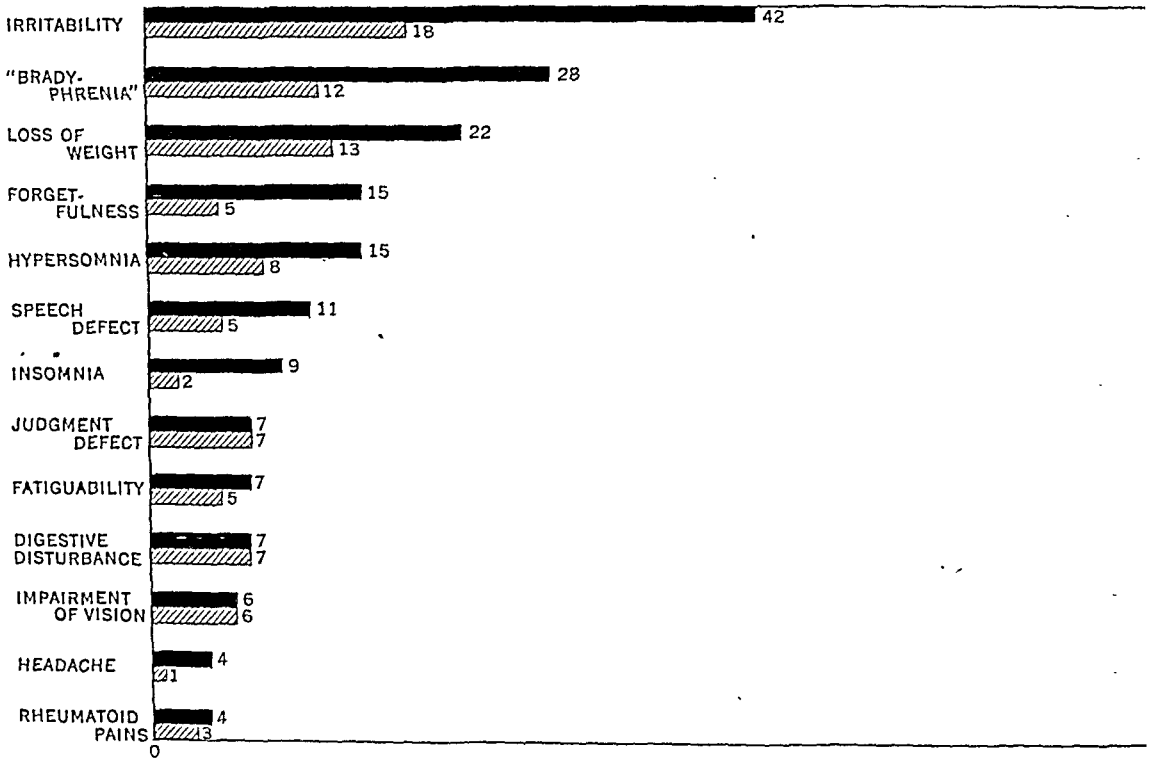


FIG. 1.—*Heavy lines:* Frequency with which a given symptom appears among the earliest changes noted. *Shaded lines:* Frequency with which a given symptom appears as the very earliest change noted.

defect, and judgment defect. The last named, though significant, is of reduced value because of the difficulty of establishing its presence; the existence of the first or second, although occurring as a relatively early symptom in only 15 per cent and 20 per cent, respectively, of this particular group of cases, should make examination of the spinal fluid imperative. Lacking in any such intrinsic diagnostic value but at least suggestive in view of its high numerical incidence as an early manifestation in more than half of the cases of this series, a history of irritability arising de novo should give sufficient ground for suspicion to demand the exclusion of general paralysis if the symptom cannot be accounted for with complete

certainty on a more obvious basis. Similarly, even though somewhat less common as an initial symptom, a history of personality change such as has been above described as an apathetic or seclusive type of reaction should be regarded in the same light. Loss of weight, although wholly undistinctive in itself, appears to be sufficiently characteristic of early general paralysis in many cases to suggest the possible presence of that disease in patients in whom other causes can be excluded. Finally, an increased tendency to sleep ranks almost with the first three symptoms just mentioned in both suggestiveness and incidence, and accordingly necessitates at least the keeping of the possibility of general paralysis in mind. The remaining symptoms—visual impairment, digestive disturbance, fatiguability, insomnia, headache, tremor, rheumatoid pains—have, of course, no diagnostic value whatever; all that can be said of them is that they occur in some incipient cases of general paralysis and that they are consistent with the presence of that disorder. But just as the possible relationship of even minor gastrointestinal symptoms to tabes has been repeatedly pointed out, so it is no less obvious that in the presence of this latter group of wholly ambiguous complaints it may become of only the greater importance at times to search elsewhere for their possible cause in neurosyphilis.

Summary. 1. If certain nervous or mental symptoms are consistent with incipient general paralysis, as certain ambiguous physical symptoms may be consistent with early tabes, then the presence of such symptoms in a patient, if they are not otherwise clearly to be accounted for, calls at least for examination of the pupils and of the knee and ankle jerks and for a Wassermann test, and raises the question, even when the evidence from these two sources is negative, of the necessity for lumbar puncture.

2. A study of the earliest symptoms which may occur in patients who later develop outspoken general paralysis, such as has been carried out in 74 male patients and here reported, may throw some light upon the symptomatic indications for the diagnostic procedures just mentioned.

3. In this study it was found that irritability holds first rank as an early symptom, since it occurred as the earliest abnormality, or one of the earliest, in 42, or 57 per cent, of the 74 cases.

4. The character change whereby an individual is reduced in activity and spontaneity, loses some of his interests, tends to withdraw into himself, and is often described as having become "quiet," is likewise a common early symptom, for it occurred in 28, or 38 per cent, of these cases.

5. Loss of weight as an early manifestation ranks third numerically. It occurred—and very often early—in 22, or 30 per cent, of this series.

6. An increased tendency to sleep, somewhat more suggestive in itself than any of the foregoing symptoms, was an early manifestation in 15 cases, or 20 per cent.

7. Speech defect, memory defect, and judgment defect have considerable diagnostic value in themselves, but they were found in this series among the earliest symptoms in only 11 cases, 15 cases, and 7 cases, respectively.

8. Visual impairment, digestive disturbance, insomnia, fatiguability, headaches, tremor, and rheumatoid pains were present as the earliest manifestations in a few cases; neurosyphilis must sometimes be considered in the differential diagnosis of these very undistinctive symptoms.

ALCOHOLIC INJECTIONS INTO NERVE TISSUES FOR THE RELIEF OF PAIN.*

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This is a report on a successful method of relieving pain applicable to a wide variety of conditions.

Ranson,[1] in his original researches on peripheral nerves, showed that a sensory peripheral nerve is made up of both medullated and nonmedullated fibers and that the nonmedullated fibers carry the pain-bearing influences (protopathic). Since these fibers are peripheral arms or projections of cells situated in the dorsal ganglia, it is quite evident that the destruction of these peripheral arms will interrupt the pathway of the afferent stimuli and thus prevent the influx of pain stimuli to the sphere of consciousness. The nonmedullated axones[2] take their origins from the small cells in the dorsal root ganglia while the medullated ones originate from the large cells.

The introduction of alcohol into a peripheral nerve produces an axonal degeneration involving mostly the small cells. The injection of 80 per cent alcohol[3] destroys not only the sensory components but also the motor components. The injection of a 60 per cent solution of alcohol, however, produces only slight transitory motor weakness, although the axonal degeneration of the afferent fibers and ganglia is quite extensive. The pathologic change[3] found in a sensory nerve and its ganglion cells following the injection of alcohol is the same as though the nerve itself had been cut, in other words, a Wallerian degeneration.

Pain in the following conditions will be discussed: (1) Laryngeal

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tuberculosis; (2) pleurisy; (3) several forms of headaches; (4) tabes with gastric crises; (5) cardiac disease; (6) pruritus ani.

Laryngeal Pain in Pulmonary Tuberculosis. The pain in laryngeal tuberculosis may be so severe as to interfere not only with rest which is vital to a tuberculous patient, but also with the ingestion of food because of the intense agony produced by swallowing. Any procedure, therefore, which offers relief for this frequent complication of pulmonary tuberculosis is a great boon to the sufferer.

In the search for relief many methods varying from mild applications to radical surgery have been tried with little success. Some of the methods briefly are: Orthoform or anesthesin insufflations, inhalation of chloretone vapors, insufflations of morphia, and submucous injections of novocain into the swollen tissues of the epiglottis and larynx. These methods have given very poor results. Operative interferences[4] (galvanocautery, curettage or amputation of the epiglottis[5]) have all ended disastrously, shortening life considerably. Another procedure[6] is to expose the superior laryngeal nerve surgically and either sever or crush it. Steinmann[7] reports 10 cases in which he resected the internal laryngeal branch with good results. Teller's[8] 12 patients obtained relief for a time, only to have the pain reappear.

In 1908, Hoffmann suggested injecting alcohol into the superior laryngeal nerve for the relief of these patients. He reported several cases with good results. His method was taken up by other workers but their reports as to success are conflicting. Lukens[9] reports 19 cases in which the shortest period of relief was three days and the longest period forty-one days after a single injection. I shall present 13 cases with the hope of encouraging the further use of this procedure and to controvert if possible a tendency to consider the method unsuccessful.

A clear conception of the anatomic course of the superior laryngeal nerve and the structures supplied by it is absolutely essential. The superior laryngeal nerve arises from the lower ganglion of the vagus, running downward and inward beneath both of the carotid arteries toward the superior horn of the thyroid cartilage About 1 cm. in front of, and a little below the cornu of the hyoid bone, the nerve divides into an internal and external branch. The internal branch enters the larynx by piercing the thyrohyoid membrane. It supplies the mucous membrane of the base of the tongue, epiglottis and the larynx. The external branch distributes its terminal filaments to the subglottic portion of the mucous membrane of the larynx and ventricle. It also gives off a few filaments to the pharyngeal plexus which supplies the constrictors of the pharynx. The ganglion of the trunk from which the superior laryngeal nerve arises, is in anatomic connection with the upper ganglion of the vagus which gives off an auricular branch. The auricular nerve courses along the inner surface of the facial

canal and terminates between the mastoid process and the external auditory meatus. The nerve supplies the skin of the posterior part of the auricle and the posterior inferior portion of the external auditory canal.

The technique for injecting the superior laryngeal nerve is as follows: The patient is placed in the dorsal recumbent position with a rolled sheet beneath the shoulders. This throws the head back and therefore moderately stretches the soft structures of the anterior aspect of the neck. The great cornu of the hyoid on the side to be injected is made more prominent by pressing with the left forefinger the great horn on the opposite side. A 5-cm. needle unattached to the syringe is inserted about 2 cm. median to and 1 cm. below the large horn of the hyoid. The needle is directed backward and slightly upward toward the great horn. The point of the needle must not be permitted to go laterally beyond a line joining the large cornu of the hyoid to that of the thyroid. Beyond this line the large bloodvessels of the neck are found. The point is pushed in for about $1\frac{1}{2}$ cm. to lodge itself between the thyrohyoid muscle and the thyrohyoid membrane. One can be certain that the nerve has been struck only when the patient has a sharp pathognomonic pain in the ear on the homologous side which he indicates, not by talking, but by raising his hand. It is rare, indeed, to pierce the nerve directly. This occurred only twice in my series. After reaching the desired area the point is gently used as a probe to explore the entire thyrohyoid area and only after the characteristic signal is given is the syringe attached to the needle and the solution injected. The patient is cautioned against swallowing while the injection is in progress. The solution is a 60 per cent alcohol (warm) containing 1 per cent cocain hydrochlorid. The cocain is used to ameliorate the immediate local pain incident to the inflammatory action of the alcohol.

Before deciding to use the alcoholic form of treatment, a careful choice of the cases must be made. Those that have difficulty in swallowing due to other causes and not attributable to pain are to be excluded. The difficulty in swallowing under such conditions may be traced directly back to other parts such as the pharyngeal muscles which are supplied by the pharyngeal plexus formed predominantly by the vagus and glossopharyngeal nerves. One should investigate these nerves and elicit the cause for this motor deficiency. Only patients with spontaneous pain and those with painful deglutition are suitable for the injection of the superior laryngeal nerve.

The injection is done on the side which is subjectively most painful and here the patient can be of the greatest service. Often the more affected side is found by careful palpation eliciting greater sensitivity and tenderness.

One of the most frequent reasons for failure is that the alcohol

is not injected directly into the nerve. The thyrohyoid space is fairly large so that the 2 cc. of the alcohol injected spreads along the fascial plane, and little, if any, is absorbed by the nerve. The thyrohyoid area must be probed lightly and patiently until the nerve is encountered. Little pain is felt once the point of the needle has passed through the skin. The syringe must not be attached to the needle before the nerve is found. It is clumsy and heavy and as a result excludes fine probing. The possibility of pharyngeal tuberculosis as a cause of pain must be remembered. This condition may also explain some of the failures. Injections into the superior laryngeal nerve under such circumstances would not alleviate the pain.

Thirteen patients with advanced pulmonary tuberculosis and with specific laryngeal tuberculosis were treated.

(*a*) In one case there was complete failure to strike the nerve although several attempts were made.

(*b*) Eight patients who had intense pain and could swallow practically no food of any kind because of pain were completely relieved. One patient was free from all discomfort for twenty-two days. The pain recurred and after another injection she was again comfortable for an additional period of fifty-nine days to the date of death. Another was absolutely free from all discomfort for fifty-three days to the date of his death. Another is completely relieved for twenty-nine days to date. Another is almost completely relieved for twenty-three days to date, another for eighty days to date, another seventy-six days to date, another seventy-six days to date and still another, ninety-six days to date

(*c*) Four patients, though relieved of pain, have difficulty in "pushing the food down," as they put it. Various degrees of this difficulty are complained of. In fact, all of the cases treated had this motor disturbance which disappeared in a day or two. These few subjects still complain of this symptom. The apparent cause for this can be explained anatomically. The superior laryngeal nerve through its external branch contributes to the formation of the pharyngeal plexus, which latter supplies the constrictors of the pharynx. Complaints of the different patients vary in intensity. One was relieved of pain for fifty-two days to the date of his death, another thirty-two days to the date of his death, another nine days to date and still another eighteen days up to the date of his death. This last was an exceedingly severe case. In fact his epiglottis had been surgically removed in another hospital because of the intense pain.

(*d*) Immediate effects after the injections are: (1) Twelve patients complained of increased local pain lasting at most two days. (2) Nearly all patients complained of immediate motor difficulty in swallowing. Most of them clear up in a few days. (3) In only

two instances has there been a slight rise in the temperature curve the day after the injection.

Pleuritic Pain in Pulmonary Tuberculosis. The following is a presentation of five cases as a preliminary report of an apparently new application of alcoholic injections into nerve tissue for the control of severe thoracic pain caused by chronic pleuritic involvement. A careful search of the literature for any reference to this method has revealed no record of its previous use.

Although it is quite true that severe, agonizing thoracic pain is not common in pulmonary tuberculosis, nevertheless, there are cases in which the distress is so severe that it responds to no treatment. The method here described offers a means for the amelioration of this intense pain.

The upper six intercostal nerves[10] supply the upper parietal costal pleura. The lower six send their intercostal fibers to the lower parietal costal pleura as well as to the parietal pleura of the diaphragm. The center of the diaphragm is supplied by the phrenic nerve which is derived mainly from the fourth cervical nerve and also from the third and fifth cervical nerves of the cervical plexus. The phrenic nerve is not only motor to the diaphragmatic muscles, but also carries afferent sensory impulses from the parietal pleura to the cervical plexus. Disease in the costal parietal pleura will transfer its effects in the form of pain to the chest wall. The site of reference will depend upon the intercostal nerves impinged. Irritation of the parietal pleura over the central portion of the diaphragm will refer the pain to the neck which is the area supplied by the third, fourth and possibly fifth cervical nerves.

Since the intercostal nerve not only hugs the under margin of the rib but also is accompanied by the intercostal artery and vein, it was considered inadvisable to attempt to inject the nerve itself along the thoracic course. The more accessible structures, however, are the dorsal ganglia or dorsal root fibers entering the ganglia. The ganglia are found in the intervertebral spaces. The thoracic nerves immediately upon emerging from the intervertebral foramina lie midway between the transverse processes of the two adjacent vertebræ and run obliquely across the intercostal spaces toward the angles of the ribs above them to enter the subcostal grooves. As the nerves course from the intervertebral foramina to the angles of the ribs, they lie on the thin aponeuroses known as the internal intercostal fasciæ. These fasciæ extend to the tubercles of the ribs. The aponeuroses are the only layers separating the nerves in this location from the pleural cavity. This anatomic fact must be borne in mind during the injection.

Technique. The intercostal nerves that are to be injected, are those whose skin areas are hyperalgesic to pin prick. After having chosen the intercostal nerves to be injected the following procedure is executed. The patient is placed on the side opposite to the one

to be injected. The knees and hips are flexed on the abdomen and the head approximated to the lower extremities. This widens the intercostal spaces. Taking the twelth rib as a landmark the intercostal spaces to be injected are carefully palpated. A line running through the midline of the vertebral spinous processes is traced on the skin. At a point 4 cm. from this line and over the ribs which are above the spaces to be injected, wheals of 2 per cent novocain are raised. The wheals act both as a local anesthetic and as landmarks. An 8-cm. needle is inserted through each wheal. The needle is directed perpendicularly to the posterior surface of the rib just above the space to be injected. As soon as the needle impinges upon the rib, it is slightly withdrawn in order to change its direction, so that its shaft points 45 degrees downward, inward and forward toward the lower border of the rib. From the lower border of the rib, the point is advanced 2 cm. further. The point finds itself between the internal and external intercostal muscles. The same technique is used to approach the several hyperalgesic intercostal nerves. The needles are then attached to a water manometer to determine whether they are in the pleural cavity. Absence of extensive oscillations indicates that the needles are not in the pleural cavity. This precaution is taken to obviate the injection of alcohol into the pleural cavity. Three to 5 cc. of novocain are then introduced through each needle. After a few minutes the areas are tested for the presence of the previous levels of hyperalgesia. The disappearance or diminution of the hyperalgesia gives concrete evidence that the points of the needles are in the correct spots. Two to 3 cc. of 80 per cent alcohol (warm) are then injected through each needle. Half of the fluid is injected without moving the needle, while the rest is distributed with a little to-and-fro movement as the point is being withdrawn. The alcohol thus deposited produces an axonal degeneration of the thoracic nerve very near to its cell body in the dorsal ganglion. Some of the alcohol may even spread along to reach the intervertebral foramen and exert its action upon the ganglion itself.

The following is a brief résumé of the salient points presented by the cases treated: The pain may be sharp, sticking or tearing in nature, usually worse at night, preventing sleep. Lying on the affected side greatly increases the pain. Coughing or active movement greatly aggravates the distress. Pressure in the intercostal spaces produces pain. In the cases treated the duration of pain ranged from five weeks to five months. The patients were all suffering from far advanced pulmonary tuberculosis showing, either by physical examination or Roentgen ray evidence, the involvement of the pleura. Neurological examination showed in all these cases definite zones of hyperalgesia involving three to four intercostal nerves.

Following the injection there was usually an increase of pain for

a day or two especially at the site of injection, due probably to the local action of the alcohol. The zones of hyperalgesia usually gave way to hypalgesia. Pain on deep pressure in the intercostal spaces over the affected area became lessened or disappeared. The patients were relieved from their pain for the following duration: One case has been relieved sixty-three days to date, another thirty-six days to date, another seventy-one days to date, another one hundred and seven days to date, and another thirty-five days to date of death.

Headaches. Three cases of severe headache were treated. Two of them complained of occipital pain due to marked involvement of the great occipital nerve from cervical spondylitis; the third had severe frontal pains due to involvement of the right supraorbital nerve.

Each case showed an area of hyperalgesia over the involved nerve. Blocking these nerves with alcohol was followed by great relief extending from ten to twelve weeks to date.

Tabes with Gastric Crises. The search for a means to control the severe agony experienced in tabetic gastric crises has finally led to the application of surgery. The surgical treatment of gastric crises depends upon the hypothesis that irritative processes going on in the sensory sympathetic fibers of the stomach, after entering the coeliac plexus in the splanchnic major nerve finally reach the spinal cord through cells found in the dorsal root ganglia. The anatomic structure suggested the idea that if the posterior roots were severed, the painful stimuli would be interrupted in their course to the spinal cord. Following the suggestion of Moskowiez, Foerster[11] in 1911 practised posterior rhizotomy. This procedure was taken up by others. Although there were many brilliant results, the failures rose to 50 per cent according to Foerster and was accompanied by a mortality of 16 per cent Many of the patients experienced relief for as long as one and a half years. The cause of failure in so many of the cases according to Purves Stewart was that with severance of the posterior roots the central stumps remained and continued to convey painful stimuli. Sicard suggested that in order to obtain better results excision or avulsion of the root ganglia would be necessary. Sicard's conception is borne out by the results obtained in trifacial neuralgia; that is, excision of the Gasserian ganglion or cutting of the central fibers is the only way to give relief in intractable trifacial neuralgia. The operation itself is extensive, severing the root segments from the fifth to the eleventh dorsal segments on one or both sides. Others practised section of the spinothalamic tracts above the fourth dorsal segment However, with the introduction of alcohol paravertebrally the following advantages are noted: A rapid minor operation is done with little or no pain and with no danger to life, and the alcohol produces not only a degenerative effect on

the dorsal roots, but also seeps up to the dorsal ganglia, producing by chemical means what Sicard suggested should be done surgically.

The following case is that of a man suffering from severe tabetic gastric crises, referred from the neurologic service for treatment.

Patient C. R., male, aged fifty years, had had gastric crises for four years. For a period of nineteen days before this treatment was instituted he was in a constant state of agony, rolling wildly in bed. The agony was scarcely controlled by 3 to 4 gr. of morphia daily. Following the paravertebral injection of alcohol into the roots of the fourth, sixth and eight dorsal segments on the right side, and the third, fifth and seventh on the left side, complete cessation of pain ensued. For forty-nine days he has now been comfortable. The morphia has been reduced to a maximum of $\frac{1}{8}$ gr. one to two times daily.

Pain in Cardiac Disease. The question of cardiac pain has always been one of intense interest engaging the attention of the internist, the neurologist and recently that of the surgeon. In recent years many operations have been devised for its relief with varied results. No agreement as to which nerve to sever has been definitely reached. The treatment is empiric and unphysiological.

An interesting case report appearing in a French journal[12] in 1923 indicated a beginning of a method that supports our present procedure. The French case reported was that of a syphilitic patient, aged forty-one years, who was suffering from aortic insufficiency and angina pectoris. The pain was located retrosternally, on the anterior surface of the left half of the chest and down the arm to the elbow. Eight centigrams of procain were injected into the second and third dorsal spinal roots. Sensory examination indicated that these levels be injected. One half hour later the patient was put through numerous tests and although the pulse rate rose from 80 to 140 beats per minute and he suffered from great shortness of breath and palpitation, there was no pain. The same efforts were repeated at the end of six hours when the effects of the procain had partially passed off. Although the characteristic pain reappeared, it was much milder. It was then decided to sever these irritable roots, but the operators were forced to stop after the second dorsal root was cut because the patient collapsed. These writers feel that the principal afferent sensory impulses pass from the heart and aorta through the ganglia and roots of the eighth cervical, and of the first, second, third and fourth dorsal nerves. The report of this case with the case to be reported by us strongly suggest the idea that pain impulses do pass to a great extent through the dorsal roots. More cases will be necessary to place this conception on a firmer basis.

The following patient was referred from the service of Dr. B. S.

Oppenheimer. It is the first case on record that has received paravertebral injection of alcohol for the relief of cardiac pain.

Patient R. C., female, aged twenty years, is suffering from aortitis and aortic insufficiency caused by congenital syphilis. Her complaints of pain began April, 1923, with pain over the precordium. In a few months the discomfort extended to the left shoulder blade and the back of the chest on the left side. The pain was sticking and constricting in character and especially worse during the night. Since April 17, 1924, the pain has been more severe. The attacks consist of paroxysms of severe sticking pain lasting a few minutes and leave in their wake a dull ache over the same area. These paroxysms are brought on with only slight exercise and as a result greatly curtailed physical activities. A zone of hyperalgesia was found extending from the fourth to the seventh dorsal segments on the left side. The following was the treatment that she was given during her stay at the hospital: (1) A course of arsphenamin and mercury salicylate which was completed October 2, 1924; (2) potassium iodid which was discontinued several months ago; (3) a series of injections with Bismogenol. Following this series of treatments she was more comfortable.

After the paravertebral injection of the fourth, fifth, sixth and seventh dorsal roots on the left side she was greatly relieved. The relief consists in her ability to carry out greatly increased physical activities with diminution in the number and severity of the attacks of pain. Before the injection of alcohol she was unable to walk more than one block because the pain was so severe that she was forced to stop. The distress lasted two to three minutes. Now she can walk from five to ten blocks and although she at times develops pain she asserts that it is so mild and fleeting that little attention is paid to it. Previous to the alcoholic injection she found that on attempting to practice on the piano more than ten to fifteen minutes, she would be forced to stop because of the agonizing pain. Now she plays at least one hour and at times longer with only an occasional pain. For the past forty-one days she has had relief.

Pruritus Ani. The lack of success which the dermatologist and proctologist have had in the treatment of pruritus ani is well substantiated in the literature. Itching is a stimulus of afferent impulses whose intensity is below that necessary to call forth a perception of pain. The general conception is that the condition is due to an involvement of the cutaneous nerve endings. This disturbance causes itching and the resulting scratching induces fibrosis in the dermis, fissures, ulcerations, and thickening of the tissue about the anal opening. Many of the cases are cured by removing the local disturbance. However, patients who have been

suffering for more than two years are often not relieved even if the local lesion is removed. Frequently in these troublesome cases a severe pruritus is present and no local lesion is seen. Treatment in these advanced cases with Roentgen ray and excision of the cutaneous nerves to the skin in the anal region have been partially successful. The case to be reported was treated by the introduction into the epidural space of a 20 per cent solution of alcohol in saline solution. The results obtained were so striking that the report of this case is of apparent value. The literature shows no reference to this application.

Patient J. W., male, aged sixty-one years, is suffering from a vascular lesion which produced a right hemiparesis. The itching about the anus began three years before his admission to the hospital. It was especially troublesome during the night. He was forced to rise and attempt to obtain relief with vigorous rubbing with a towel. Immediately after having a bowel movement this itch would become especially severe and persist from a half to one and a half hours. He was admitted to the neurologic wards at Montefiore Hospital one and a half years ago. From the date of his admission his complaints concerning the itching were constant and pitiable. His sleep during the night was greatly disturbed. He was seen by the dermatologist and prescribed for without avail. Following our suggestion an epidural injection of 80 cc. of saline and novocain was made with no relief at all. On May 12, 1925, eighteen days ago, a solution of 20 per cent alcohol in saline to make a total quantity of 75 cc. was introduced into the epidural space. He was immediately relieved. That was eighteen days ago and he is still comfortable. This method might be of special value in those cases in which the itching induces scratching and as a result inhibits the local healing power. The controlling of the itch together with the local treatment should be of great aid in helping these patients.

Summary. I have attempted to present a series of cases, diverse in nature, in which alcoholic injections into the nerves were made, in order to obtain relief from excruciating pain.

The cases in which thoracic and cardiac pain was relieved are presented merely as a preliminary report.

The alcoholic injections into nerve tissues for the relief of pain have been in our hands a valuable therapeutic procedure.

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FUNCTION OF THE AUTOGENOUS KIDNEY TRANSPLANT.

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Since the development of a successful method of bloodvessel suture has made transplantation of whole organs possible, many experimental studies have been made on the transplantation of the kidney. The possibility of transplanting organs by vascular anastomosis has not only been proved, but a reliable surgical technique for the purpose has been established. This method has opened a new and broad field for experimental studies on the kidney with an approach to some very interesting problems. Many are mainly of interest from the physiologic standpoint, others chiefly of surgical interest. One suggestion of practical significance was the long-cherished surgical dream of possibly substituting a healthy organ for a diseased one. The perfection of a method of bloodvessel anastomosis and improvements in surgical technique seemed to offer a rapid realization of this dream. In regard to the kidney it was readily shown that autotransplantation of the organ could be successfully accomplished, and in a high percentage of instances a good functional result secured. However, for it to have any practical value it is necessary to employ homogenous or heterogenous transplants, and the results of such transplantation showed that there were seemingly other factors involved than those encountered with the autogenous transplant.

This investigation was undertaken to advance further experimental explanation of this difference between the autogenous and the homogenous transplant and to investigate the functions of the autogenous kidney transplant in detail, by comparing them with those of the other normal kidney, by observing the function of the transplant before and after removal of the untouched sister organ and by observing at the same time the general condition of the animal. Also it was hoped to establish a definite standard of function of the autogenous transplanted kidney for comparison with the function of the homogenous transplanted kidney, as presented in the succeeding paper.

Review of Previous Work. As more than thirty studies on autotransplantation of the kidney have been published, it is only possible to present their general results. Various sites have been employed for the attachment of the transplant, including the neck, inguinal region and various points within the abdomen. In accordance with the site chosen, either the common carotid artery and jugular vein in the neck, femoral vessels in the inguinal region, or the iliac, splenic or the renal vessels in the abdomen were used for anastomosis to the renal artery and vein of the transplant. In some investigations the organ has been left *in situ* and the renal vessels severed and anastomosed, or both the aorta and vena cava have been severed above and below the entrance of the renal vessels and anastomosed. The simple end-to-end method of suturing vessels has been most often used and considered the best. For the management of the ureter of the transplant, in order to drain the urine properly or to serve the purpose of observation, the ureteral end was sutured directly to the skin, the wall of the esophagus or the wall of the bladder. The first investigators contented themselves with demonstrating the possibility of transplanting the kidney, establishing the proper surgical technique, observing the excretion of urine from the transplant in its new situation and maintaining the life of the animal by the transplanted kidney alone. However, with the elaboration of a successful surgical technique for transplantation of the kidney, histologic and functional studies become the center of interest, because no crucial evaluation of the results can be obtained otherwise. The latter investigations have scarcely done more than show the magnitude of the problem. The recent development of modern methods of analyzing chemically, particularly by micromethods, the principal constituents of urine and blood, together with the advent of reliable methods for testing the functional efficiency of the kidney, have made a more detailed study of the effect of transplantation of this organ of great interest and possibly of practical value.

Operative Technic and Method of Observation. All experiments were performed on active, well-nourished mongrels, weighing about 10 kg. Animals of good disposition were chosen to insure ease in handling them, and short-haired dogs were selected so as to minimize the danger of infection of the wound by hair. Whenever possible, female animals were chosen, as urine could be obtained from the bladder without difficulty. The neck of the animal was used as the site for transplantation, as the excretion from the transplant could be readily observed, and the urine could be collected without soiling, and separately from that of the other kidney. Thus the function of both kidneys could be compared, and the change of function of the autotransplant before and after the removal of the untouched kidney could be accurately followed (Fig. 1).

The operations were carried out under ether anesthesia, with the strict aseptic technique which is necessary to insure success in the experiment. The bloodvessels of the neck were first prepared, and then the left kidney, after being excised through an incision in the median line, was carefully wrapped in a warm salt pack and transferred to the neck for future engrafting. The renal artery was anastomosed to the common carotid, and the renal vein to the external jugular vein, the usual end-to-end method of suturing bloodvessels being employed, as described by Carrel and Guthrie. The ureter was brought to the outside through a small separate



FIG. 1.—(Dog H-745). Photograph showing method of collection of urine specimens from the transplanted kidneys in the neck. The right kidney (above) was transplanted four days before, and the left kidney (below) fifty-one days before this picture was taken.

stab wound in the skin, and the kidney placed in a muscle pocket in the region of the carotid sheath, after the reëstablishment of circulation through the organ was assured. These procedures were always followed with painstaking care, in order to avoid hemorrhage, traumatization of bloodvessels or other harmful effects on the transplant. Further details of the technic are not given, since it has been described by Guthrie, Williamson and others.[5]

As a routine the wounds of the neck and the abdomen were closed without drainage. Collodion gauze dressing was used on all except the stab wound through which the ureter passed. A small sterilized ureteral catheter, the tip of which had been smeared with

vaselin, was inserted into the ureter to the pelvis of the transplant. The distal end of the ureter was tied around with No. 00 catgut to hold the catheter in position and control the bleeding from the ureteral bloodvessels. This ureteral stump was allowed to protrude from the stab wound to a length of from 1.5 to 2 cm. It was not sutured to the skin because the neck and the ureter were usually swollen more or less for two or three days after the operation, and also because the movement of the neck immediately after the transplantation might cause some slight dislocation. If the ureteral stump were fastened to the skin the ureter might sometimes be drawn too tight or be kinked, and thus obstruct the blood supply to the kidney or prevent the free drainage of excreted urine. The protruding part of the ureter was pasted with sterilized vaselin and covered with a small gauze sponge for protection until the animal recovered from the anesthesia, soon after which it was removed. For several days following the operation the ureter and the surrounding part of the skin were frequently treated with a wet dressing of Dakin's solution, as they were quite often contaminated superficially by soiling, especially with urine.

The catheter was usually left in position from forty-eight to seventy-two hours after the operation, because drainage of the excreted urine was frequently hindered by swelling, both of the ureter itself and of the surrounding tissues. However, by the time the adhesion and adaptation of the ureter to the surrounding tissues was established the further drainage of urine to the outside readily took place without the catheter. In spite of all precautions, a small amount of blood dripping over the end of the catheter sometimes clotted at the opening, or mucus excreted from the pelvis plugged the lumen of the catheter. When this occurred the catheter was washed with sterilized salt solution or distilled water, or was changed. The catheter could often be kept patulous by giving an abundant supply of water or milk to the animal and thus encouraging diuresis.

At the operation the excised kidney looked pale yellowish and flabby before reëstablishment of circulation through it; but when the anastomosis of bloodvessels was completed the kidney soon assumed a normal reddish color and normal consistency, and showed apparent pulsation of the artery and engorgement of the vein. It should be mentioned that marked tenseness of the kidney was evident immediately after the reëstablishment of the circulation, but after one or two minutes it rapidly passed away. By the time the wound was closed frequently small amounts of urine were being discharged from the catheter in the ureter.

During the experiment, after transplantation had been performed, the diet was regulated, specimens of blood and urine were taken at various times for chemical analysis and observations on the excretion of the transplant frequently made. As good-natured dogs

were chosen for the experiments, gentle handling and loose tying of the animal on the observation table, which had been especially constructed for this work, soon accustomed the animal to lie quietly and with ease for long periods. Observation was thus facilitated, and chances of disturbance of the transplant or interference with the results of the experiments were minimized. Thus, the collection of urine from the transplant into the test tube through a clean, short ureteral catheter, the catheterization of the bladder on every necessary occasion, and the injection of dye or drugs were carried out without difficulty (Fig. 1).

The time taken for the transplantation was usually about an hour and thirty minutes, but the time during which the renal circulation was interrupted was between twenty and thirty minutes, reckoned as the time which elapsed between the clamping of the renal bloodvessels and the reëstablishment of the circulation through the carotid artery and jugular vein. As the experiments of autotransplantation of the kidney were used to develop technique for the second phase of the problem, that of homotransplantation, my percentage of successes was not as high as if the series had been started after the requisite technique and skill had been acquired. For this reason the number of experiments and percentage of successes are not given. While many of the experiments were partially successful, detailed studies have been made on eight autotransplanted kidneys.

The following tests were made:

CHEMICAL ANALYSIS OF BLOOD AND URINE.

Blood.	Urine.
Nonprotein nitrogen (Folin and Wu)	Total nitrogen (Folin and Denis)
Urea nitrogen (Folin)	Urea nitrogen (Van Slyke and Cullen)
Creatinin (Folin)	Ammonia nitrogen (Folin and Farmer)
Chlorid (Whitehorn)	Chlorid (Whitehorn)
	Sugar (Benedict)
	Reaction (Litmus paper)
	Phenolsulphonephthalein (Maclean, using Kober's colorimeter)

Results of Experiment. In common with most investigators, I occasionally encountered thrombosis of anastomosed bloodvessels, infection of the wound, as well as of the transplant itself, displacement of the kidney in the new location, kinking of the ureter and retraction of the protruding ureteral stump from the stab wound. Those are the main troubles which lead to failure of the experiments immediately after transplantation. With mastery of the surgical technique, however, and the carrying out of proper care for the treatment of wounds and of the animals themselves, it was possible to maintain a kidney transplant successfully, even in the neck of the dog, with results much the same as those of Dederer and Williamson. Although in the neck the persistence of the kidney may not be per-

manent, still the duration (over ten months) of its function is quite sufficient for the investigation of many problems concerning transplantation and functional activity of the kidney.

The circulation of the kidney is interrupted for a certain period (at the most, thirty-five minutes), but the organ can stand, and apparently recover from, such effects if accurate technique and proper care are instituted. Such a well-transplanted kidney in the neck of the animal carries out its normal functions thereafter for months, while the other kidney functions in the abdomen. Even after excision of the other kidney, whether within a few days or after a fairly long time (over six months), the transplanted kidney is able alone to maintain the normal life of the animal for a long period (four months). The transplant responds, therefore, to the excessive demand set up by experimental procedures, as well as to physiologic processes. This fact shows that, although the kidney is a very delicate parenchymatous organ and sensitive to interruption of its circulation, as proved by certain investigators, still it has a power of resistance and an ability to recover if the interruption is limited to a certain period of time.

Urine from the transplants, obtained both before and after the removal of the unmolested kidney, is fairly normal so far as its concentration and main constituents are concerned. Albumin in the urine from the transplant is found in most cases immediately following transplantation; it soon disappears, however, if transplantation and the postoperative course are uneventful Urine from the transplant is alkaline during the immediate period after transplantation, but later it is often acid. Concentration of chlorid is usually much higher than that in urine from the untouched kidney during the first period after the operation, but later this difference is not so marked. Those changes of reaction and of concentration of chlorid resemble the results from the urine of denervated kidneys. On the other hand, excretion of nitrogenous substances, of phenolsulphonephthalein, as well as of sugar after injection of phlorhizin, is in most cases less in the urine from the transplant than in the urine from the sister organ in the abdomen, both immediately after transplantation and later.

The transplant excretes phenolsulphonephthalein, in a small percentage and with slight delay of onset, immediately after the transplantation. Parallel with recovery from the immediate effects of the operation, however, elimination of the dye increases, not only in quantity but also in promptness, on the average two minutes after its intravenous injection.

After the excision of the remaining kidney an apparent increase in the rate of excretion from the transplant is manifested, not only by the volume of urine excreted in a certain period of time, but also by the excretion of phenolsulphonephthalein. The absolute amounts of the dye vary in each case, according to the condition of

the transplant. It was often discovered on operating that the kidney to be used for the transplant showed some pathologic condition, such as scarring due to infection or advanced age of the animal. However, if the organ is normal, and has been successfully transplanted, the elimination of the phenolsulphonephthalein soon reaches the normal limit of excretion through both kidneys, although the absolute amount of excretion during the first hour after the injection (the highest output, 55 per cent) always remains slightly diminished compared to the amount excreted by both kidneys after transplantation. But concentration and onset of excretion of phenolsulphonephthalein show no marked change until hydronephrosis and infection have caused dysfunction of the transplant. At this time both decrease of excretion and delay in appearance are noted.

Furthermore, the equilibrium of nitrogenous constituents, as well as the amount of chlorid and sugar in the blood, shows no remarkable change before and after transplantation, or even after excision of the remaining kidney. It can be concluded that the excretory function of the transplanted kidney alone is sufficient to keep them normal as long as the transplant is in full activity. Near the end of life, in such animals as suffer from disease of the transplanted kidney, those nitrogenous constituents of the blood accumulate until the animal finally dies with the typical symptoms of uremia. Excretion and character of urine change at this time also, for albumin casts and pus cells appear and increase, while the amount of urine decreases.

The regulatory activity and the response of the transplanted kidney to the demand set up by experimental procedures, such as the injection of phlorhizin, the administration of such pharmacologic substances as sodium salicylate, the increased intake of water or physiologic solution of sodium chlorid or glucose by mouth or by intravenous injection, are fairly normal when the transplant is in good condition. The diuresis caused by water or physiologic salt solution, which is administered through the mouth and absorbed from the alimentary tract, leads to an increase of urine which begins in from twenty to thirty minutes after these substances are swallowed, reaches its maximum at one or two hours and then falls slowly to normal.

These results coincide with the observations on diuresis made by other investigators in the excretory process of normal kidneys. Also the relation of excretion of total nitrogen and chlorid in the urine during such diuresis is nearly the same as that experimentally observed in the normal kidney. When water is given by mouth in large quantity the percentage of nitrogenous constituents falls, whereas when physiologic salt solution is given in the same way neither the nitrogenous constituents nor water is much affected, although the percentage of chlorid relatively rises.

Peristalsis of the ureter is observed during the operation, even after the kidney is removed and before the circulation through the organ is yet reëstablished. However, after reëstablishment of the circulation it shows more activity than during the interruption of blood supply. The periodic flow of urine from the distal opening of the ureter of the transplant, and even the expulsion of the inserted catheter, are also observed, beginning several days after transplantation, and this periodic flow of urine increases to such a marked degree at last that the ureter really squirts urine in a thin stream about a half foot from the animal, at frequent intervals. This is especially noticeable near the end of the animal's life, a fact which coincides with the observations of Dederer and Williamson.

The well-functioning kidney transplants have a practically normal anatomic appearance of the vascular and tubular elements, although some scarring may be found in a few areas (Figs. 2 to 5). On the other hand, those of the disabled transplant show hydronephrosis and infection. The hydronephrosis usually does not proceed to the extreme extent of destroying parenchyma mechanically, but rather infection of the renal tissue in the form of pyelonephritis prevails, as manifested by cellular infiltration, proliferation of connective tissue and destruction of the essential elements of renal tissue. However, the glomerular tufts are relatively well preserved, even while the cellular elements of the tubules fall into marked atrophy, degeneration and even necrosis.

Discussion. The proper choice of the site for transplantation of the kidney is a most important factor in the success of the operation, as well as in the restitution of the function of the organ. However, if reimplantation in the natural site alone is favorable for the maintenance and the persistence of good function of the kidney, as some investigators concluded, the procedure is robbed to a large extent of its experimental value as well as its clinical application. The feasibility of transplantation of the kidney as an actual operation should be so firmly established as to make it applicable even in the presence of certain differences of blood pressure and blood supply, lack of original protection by surrounding organs and exposure to certain mechanical insults and to the infection which must be expected in the cervical region. Success with transplantation of the kidney in the neck of the dog may establish the feasibility and value of the operation not only for experimental, but also for clinical, purposes, although the latter may be only rarely carried out.

It is also desirable to determine whether function of the transplant continues in the new location, coëxistently with the normal kidney in the abdomen or not, and if it does it would possibly be of clinical value to know how long it is normally maintained. Some investigators have inclined to the view that the transplant does not coöperate with its sister organ, and that it loses its activity

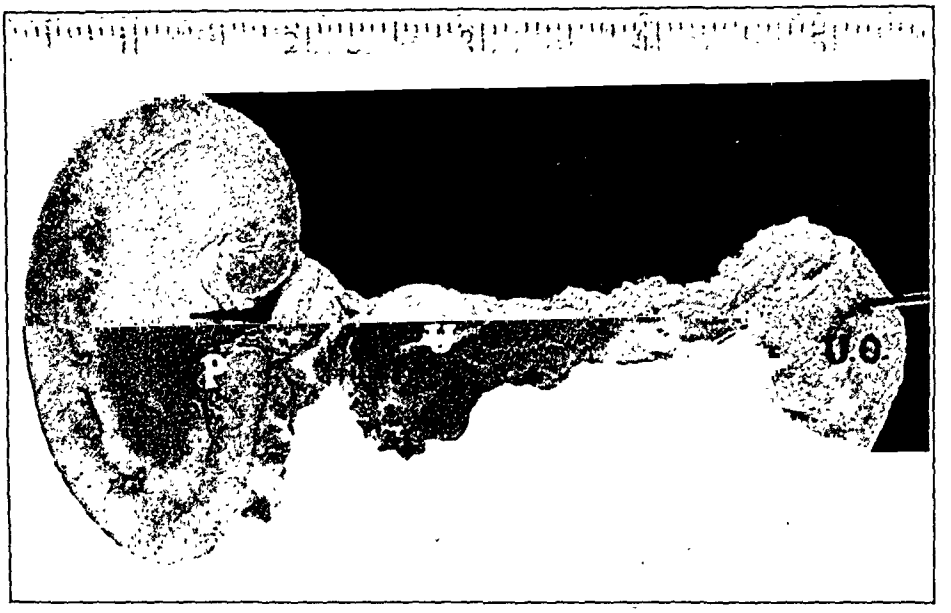


FIG. 2.—(Dog. H-351). The gross specimen of a successfully transplanted kidney that had functioned normally for ten months; the animal was killed at the end of this time. Normal appearance of the cut surface of the kidney, slightly dilated pelvis (P), perfectly patent ureter (U), and ureteral opening in the skin (U.O.).



FIG. 3.—(Dog. H-351). Photograph of kidney and vessels showing good healing of the anastomosed bloodvessels of the transplanted kidney. The sutured parts (dark mark indicated by double headed arrow) of artery *A* and vein *V* show smooth luminal surfaces, slight thickening of perivascular connective tissue, but no stenosis.

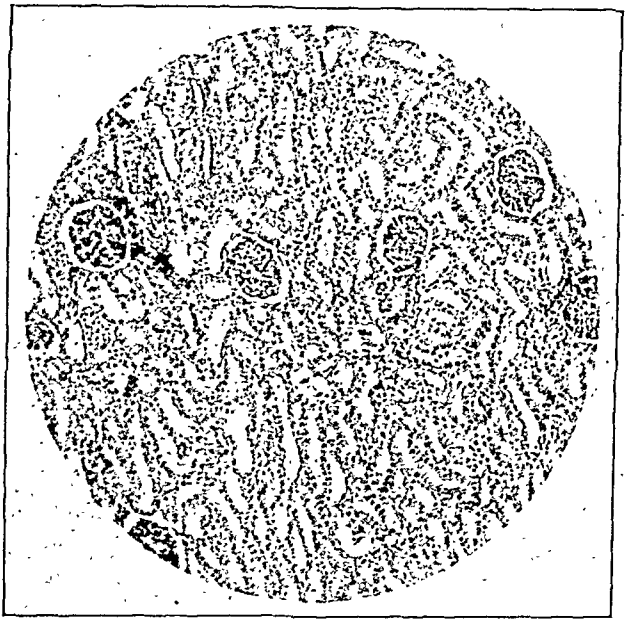


FIG. 4.—(Dog H-351). Photomicrograph of section from the transplanted (left) kidney that functioned normally in the neck for more than six months (coëxisting with *the right kidney in the abdomen), and after the removal of the latter, 121 days alone.* Apparent hypertrophy of glomerular tufts as well as tubular cells, but structure normal. (Compare with Fig. 5.) (× 60.)

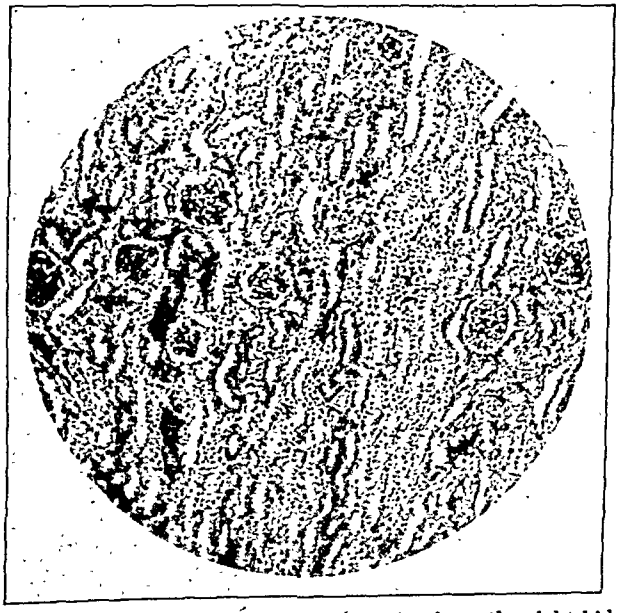


FIG. 5.—(Dog H-351). Photomicrograph of section from the right kidney which was removed from the abdomen 189 days after the left kidney had been transplanted. Renal tissue is normal. (× 60.)

of function by atrophy, owing to a decrease or a lack of normal functional stimulus, unless the other kidney is removed shortly after the transplantation. In one of our experiments the remaining normal kidney was removed from one dog one hundred and eighty-nine days after the transplantation, and the animal was surviving in good health four months later.

The existence and extent of the reserve functional power of the kidney have often been discussed, their proof being as important a question in the kidney as it is in the heart. The present experiments have not answered the question whether this compensation is borne by the functional reserve power of the kidney alone, or whether by the help of other organs. The results of urinalysis and functional tests show, however, that the transplanted kidney soon responds to the physiologic demands and even to the excessive call occasioned by experimental procedures after ablation of the other kidney.

The literature on the influence of the renal nerve on secretion is voluminous, and many workers have studied the efficiency of the denervated kidney. The conclusions of these investigators can be arranged in two classes: The first assumes the existence of secretory fibers in the extrinsic nerve; the second denies it. The most reliable method of excluding the influence of the nervous system through the extrinsic nerve of the kidney may be the transplantation of the kidney in a different site, since the possibility of regeneration of nerve is not entirely excluded in the case of reimplantation. My results lead to the conclusion that the extrinsic nerve supply plays a minor and not an essential part in renal function.

Many factors, such as changes in the circulation or the mechanical condition of the outflow of the urine, or the direct pressure on the kidney itself, as well as denervation, affect both the quantity and quality of the urine excreted by the transplanted kidney. The results of the experimental and clinical observations do not coincide in all details. In the transplantation of the kidney some change of local blood pressure or blood supply to the transplant is likely to occur, as the range of blood pressure between renal artery and vein is different from the range between the carotid artery and jugular vein. Also alteration of the normal outflow of urine from the kidney may be occasioned by the insertion of a catheter into the ureter immediately after the operation and later by the obstruction of free drainage that is caused by the contraction of the muscles of the neck and the cicatricial constriction of the skin around the ureteral opening. The possibility of difference of the direct pressure on the kidney by the surrounding tissues should also be considered, as the kidney is removed from the abdomen and put into the muscle pocket in the region of the carotid sheath. Furthermore, the metabolic, circulatory and other pro-

cesses of the living organism, which go to make up the general condition of the animal, may have an influence on the renal function and change the quantity and the quality of the urine from the transplant. However, it was observed that the transplants excreted urine which was always nearly normal in physical properties and chemical constitution. Therefore, it can be concluded that, in spite of adverse influences, the transplanted kidney shows as much power of adjustment as the normal kidney.

The innervation of the muscles of the renal pelvis and the ureter by the extrinsic nerve has been discussed by many investigators from the anatomic and physiologic standpoints, and, since the question has not yet been decided, the paralysis of the ureteral muscles, occasioned by the loss of innervation through the extrinsic nerve supply, is accounted a cause of hydronephrosis by some clinicians and investigators. In some of my transplants hydronephrosis was observed, but at the same time marked activity of peristalsis of the ureter was noted which increased enough to eject urine in a fairly long stream at frequent intervals. This hydronephrosis in the transplants may be attributed mostly to mechanical factors, such as the obstruction of free drainage by the contraction of the muscles of the neck as the animal moves its head from side to side, or by the cicatricial constriction of the skin around the ureter, with probably actual atresia of the ureter. The atresia of the ureter did not appear to be primarily due to infection.

Conclusions. 1. The successful autogenous kidney transplant in the neck of the dog functions for months in a practically normal manner, coëxisting with the normal kidney in the abdomen; it also maintains the life of the animal in good health for a fairly long time after the excision of the other kidney, while preserving its own functional activity. One transplanted kidney was in good condition four months after removal of the other kidney.

2. The neck can be used as a site for transplantation, and the kidney can be there utilized for the study of certain renal functions, as well as the physiologic activity of the transplant itself.

3. Analysis of chemical constituents of urine from the transplant as well as various functional tests made on it, simultaneously with the investigation of the remaining normal kidney in the abdomen or after the removal of this sister organ, shows a fairly normal kidney function.

4. An apparently compensatory activity of the transplant is observed after ablation of the other kidney.

5. The extrinsic nerve supply to the kidney and the ureter plays a minor and unessential part in their function, as the transplanted kidney functions equally well in the new location, and the renal pelvis and ureter show even an increased peristalsis.

6. The ultimate failure of the function of these autogenous kidney transplants, which have been transplanted successfully in the neck

and functioned a fairly long while, seems to be caused by hydronephrosis and infection, mainly incurred by mechanical insult in the new location.

7. These results of autogenous transplantation of the kidney may serve as a controlling experiment for renal transplantation of other kinds, such as the homogenous or heterogenous.

TABLE I.—CHEMICAL ANALYSIS OF BLOOD AND FUNCTIONAL TEST ON TRANSPLANT AFTER TRANSPLANTATION OF ONE KIDNEY AND EXCISION OF THE OTHER.*

Date, 1924.	Mg. for each 100 cc.			Percentage		Output of phenolsulphonephthalein in first hour, per cent.	Comments.
	Non-protein N.	Urea N.	Creatinin.	Chlorids.	Sugar.		
Nov. 26	24	7.4	1.3	0.42	0.08	..	Before transplantation.
Dec. 1	...	.....	...	....	....	4	
Dec. 8	...	.....	...	....	....	13	
Dec. 11	21	6.6	1.2	0.49	0.07	..	Before excision of the other kidney.
Dec. 13	74	25.0	2.9	0.47	0.06	26	Good secretion from the transplant.
Dec. 26	73	17.0	1.7	0.49	0.07	30	
1925.							
Jan. 11	...	17.3	1.6	0.47	0.07		
Jan. 14	222	117.6	...	0.36	0.16	Trace	Albumin, pus cells, casts in urine and uremic symptoms; animal died January 15, 1925.

* Transplantation of the kidney (Dog G-443) was performed November 26, 1924, and excision of the other kidney was performed December 11, 1924.

TABLE II.—CHEMICAL ANALYSIS OF BLOOD AND FUNCTIONAL TEST ON TRANSPLANT BEFORE AND AFTER EXCISION OF THE REMAINING KIDNEY IN THE ABDOMEN.*

Date, 1925.	Mg. for each 100 cc.			Percentage.		Output of phenolsulphonephthalein in first hour,† per cent.	Comments.
	Non-protein N.	Urea N.	Creatinin.	Chlorids.	Sugar.		
Jan. 19	32	5.2	1.3	0.45	0.08	..	Before excision of the other kidney.
Jan. 20	37	9.1	1.4	0.47	....	53	After excision of the other kidney.
Jan. 30	28	8.9	1.2	0.48	....	50	
Mar. 23	49	9.9	1.5	0.49	0.07	55	
April 5	52	13.8	2.1	0.52	0.08	51	
April 13	49	15.5	2.1	0.46	0.07	55	
April 20	42	4.3	1.4	0.50	0.07	..	
April 27	38	13.1	1.5	0.49	0.07	53	
May 4	44	5.9	1.7	0.48	0.08	53	
May 11	40	11.9	1.5	0.51	0.09	55	Pyelography of the transplant.
May 18	36	8.7	1.3	0.51	0.08	46	
May 20	28	10.4	1.3	0.47	0.08	..	Animal was killed by bleeding under ether.

* Transplantation of the kidney (Dog H-351) was performed July 14, 1924, and excision of the other kidney was performed January 19, 1925.

† It should be noted that the output of phenolsulphonephthalein from the transplant was 25 per cent and that from the other kidney 35 per cent before excision of the latter.

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FUNCTION OF THE HOMOGENOUS KIDNEY TRANSPLANT.

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Since many experimental studies proved that autogenous transplantations of the kidney could be made successfully, the attempt has been made, in anticipation of the clinical application of the operation, to replace disabled kidneys by the transplantation of others with normal function.

There are two sources of material for transplants for this purpose: One the homogenous and the other the heterogenous. The heterotransplant may be the more favorable source from the clinical point of view, as the homotransplant is not very convenient, not only because the sacrifice of a valuable organ risks the vitality of the donor, but also because the difficulty of securing such a transplant is greater under any circumstances. Nevertheless, heterogenous transplantation of the kidney has never been successfully accomplished because there are certain limitations and complicated biologic relationships between the donor and the recipient which are still unknown.[17, 18] While homogenous transplantation of the kidney is not so limited as heterogenous in this respect, decided success has not as yet been positively obtained, and many phenomena still remain obscure.

The present experimental study investigates the functional process of the homotransplant and its effect on the recipient. Before details are discussed the results and opinions of previous workers in this line and the hitherto unsolved problems will be reviewed.

Review of Previous Work. The first report of the homogenous transplantation of the kidney through the anastomosis of bloodvessels was made by Ullman and Decastello in 1902; they observed the excretion of urine from the transplanted kidney in the dog. Later, Floresco, Carrel and Guthrie, Capelle, Carrel, Unger, Borst and Enderlen, Guthrie, Villard and Tavenier, Villard and Perrin, Ingebrigsten, Dederer, Williamson, Holloway and Avramovici published the results of their investigation. Many of these investigators experimented with the autogenous transplantation of the kidney at the same time, in order to establish controls for the study of homogenous transplantation. Floresco, Carrel and Guthrie directed their investigations especially toward the establishment of surgical technique for this purpose, endeavoring to ascertain the proper site for the transplant, to improve methods for anastomosing bloodvessels, or to secure the appropriate management of the ureter of the transplant; Carrel's results were the most valuable. The dog and the cat were both used in these studies. As for the site for the transplant, every location that had been used in the autogenous transplantation was employed, such as the neck, the inguinal region and various sites in the abdomen. During the progress of the investigation of homogenous transplantation a special operation, called mass transplantation of the kidney, was worked out by Carrel and Guthrie, in order to study more closely the reconstruction of the urinary system and the functional efficiency of the homotransplant. They found in the simple transplantation certain mechanical troubles which made the experiment unsuited for use in investigation, but in subsequent researches both simple and mass transplantation of the organ were employed. The purpose of these studies was not only to demonstrate the possibility of homogenous transplantation of the kidney, but to compare the length of survival of such a kidney transplant or the life of the animal after transplantation, as well as the functional behavior of the transplant and the general condition of the recipient, with the results of similar studies on autogenous transplantation.

Concerning the length of survival and function of the homotransplant, Floresco observed that the homotransplants in the neck functioned for periods of from two to nine days, after which in every case they were destroyed by infection and necrosis. Dederer, who transplanted a kidney from one dog into the neck of another dog of the same litter, found that the homotransplant continued to function twenty-six days after operation, at the same time with the recipient's own kidneys, until the recipient died from intercurrent distemper. But this was regarded as rather a special case, as the transplantation was carried out between animals of close kinship. Williamson, who investigated this subject more thoroughly than the previous workers, comparing the length of survival and function of the autotransplant and homotransplant in the neck of the dog,

found that the homotransplant functioned for periods of from one to ten days (an average of four days), while the autotransplant functioned for several months, maintaining the life of the animal in a practically normal manner even after removal of the remaining normal kidney. The ultimate failure of the functional activity of the autotransplant was found to be caused by atresia of the ureter and hydronephrosis with a complication of infection, while that of the homotransplant was not due to such mechanical factors. Borst and Enderlen also found similar differences between the autotransplant and the homotransplant. They performed both transplantations with the same technique and in the same site in the abdomen, using the splenic bloodvessels for anastomosis to the renal artery and vein. The length of survival of the homotransplant was fourteen days, after which the kidney was in a necrotic condition, whereas the autotransplant functioned and maintained the life of the animal for one hundred and eighteen days with persistence of the normal renal structure. Such a difference in the length of survival of the two transplants was also evident in the results of other workers (Dederer, Villard, Carrel and Guthrie), although the comparison between autogenous and homogenous transplantation was not the purpose of their studies. As the result of mass transplantation, in which case the life of the animal depends on the functional activity of transplanted kidneys, Carrel and Guthrie found the shortest length of life after operation to be three days and the longest thirty-six days (average of sixteen days), at the end of which time the animals died from hydronephrosis, intestinal compression by peritoneal adhesion, phlegmon, puerperal infection, or compression of the renal vein by the connective tissue of organized hematomas. Unger, who also performed many experiments on cats and dogs, obtained no better results than Carrel. The longest time of survival among his animals was eighteen days after transplantation in one case; all the others died within shorter periods. The causes of death were thrombosis of the aorta and vena cava, peritonitis, postoperative hemorrhage, or diseases that, although obscure, did not seem to be uremia. Avramovici kept an animal alive seventy-one days, but other investigators also observed that the length of life of an animal after transplantation was short, eighteen days being the longest period observed by Borst and Enderlen, and twenty-four days by Ingebrigsten.

Carrel found fairly normal structure in some cases of transplanted kidneys, and in others the picture of interstitial nephritis. Borst and Enderlen, on the other hand, observed remarkable degenerative changes and necrosis of renal tissue, and Ingebrigsten a pronounced picture of acute nephritis with lymphocytic infiltration in the homotransplants. Carrel and Guthrie, investigating the functional efficiency of the homotransplant, observed in the mass transplantation experiments slight variations in the composi-

tion and total amount of the urine. All such variations, however, were entirely within normal limits, except the presence of coagulable protein, but the result obtained by Williamson, who tested the excretion of phenolsulphonephthalein from the transplant, and determined the nitrogenous elements in the blood of the recipient, established the fact that for a few days the homotransplant functioned similarly to the autotransplant, after which its activity failed. While all three kidneys were functioning, however, a sharp reduction was noticed in the nitrogenous elements of the blood urea and creatinin in the recipient. Holloway, who studied the influence of diuretics on the excretion of autotransplants and homotransplants, arrived at the same conclusion as Williamson.

Thus, from a general review of previous investigators, one perceives that conclusive success with transplantation of the homogenous kidney was not attained by previous workers, although the possibility of such transplantation and a certain amount of functional activity of the homotransplant were assured. The most marked fact observed by previous investigators is the difference in the length of survival and in the functional efficiency between the autogenous and the homogenous transplants. The length of survival of the homotransplant varied greatly, according to the different investigators, although they employed practically the same technique which they had previously established for autogenous transplantation, and which had been attended by good results in establishing the control for the experiment of homogenous transplantation.

Certain investigators attributed the different results and the varying behavior of autogenous and homogenous kidney transplants mainly to imperfection in surgical technique, such as interruption of the circulation, perfusion of the organ during the operation, or to mechanical factors, such as thrombosis of the bloodvessels, obstruction of the ureter, or else to infection after transplantation, to which the autotransplant also is subject, although to a lesser degree than the homotransplant. On the other hand, other investigators accounted for the divergencies in the results not so much by such surgical or mechanical factors, as by the fundamental biologic differences existing between donor and recipient.

The histologic picture and the functional efficiency of the transplant which were observed by the workers at different times after transplantation also resulted variously, and, in consequence, their interpretation differs widely. According to some investigators, the functional efficiency, as determined by frequent urinalysis and by observation of the general condition of the recipient, remained normal until the animal succumbed to intercurrent disorders, and wherever the function was modified in some measure they attributed it to errors in technique or other mechanical factors. They applied the same interpretation to the findings in the histologic

pictures of the homotransplants, some of which were nearly normal; in others which showed some interstitial and epithelial lesions they attributed the pathologic changes to perfusion, denervation or imperfect restitution of the anastomosed bloodvessels or of the ureter. Other workers, finding similar variations, were inclined to attribute these changes mainly to the biologic factor. The divergent results and opinions of previous investigators suggest that there are two phases of the experiment to be determined preliminary to the solution of the problems of transplantation. One is the investigation of the general underlying principle of biologic relationship between the donor and the recipient in transplantation, which may not be restricted to the scope of transplantation alone, and the other is a further attempt to improve technique and an exact comparison of the behavior of the autotransplant and the homotransplant by functional and histologic examination, considering the effect on both transplant and recipient.

Operative Technique and Method of Observation. The operative and routine procedures of these experiments were exactly the same as given in the preceding paper,[15] except, of course, that the transplanted kidney was obtained from another animal than the recipient. Fourteen homogenous transplantations of the kidney were done. Two of these were technical failures; four other experiments were complicated by postoperative sequelæ; eight of the experiments were technically successful in every respect.

Results of Experiments. The surgical technique of the operation of the homogenous transplantation was no more difficult than that of the autogenous. On the contrary, it seemed rather easier to carry out, as an adequately-sized kidney transplant could be obtained by choosing the donor, and the nephrectomy for obtaining the transplant in the same animal through laparotomy was not necessary; the animal therefore sustained less operative trauma and recovered more quickly from the immediate effect of the operation than after autogenous transplantation. The postoperative sequelæ, such as thrombosis of the anastomosed bloodvessels, obstruction of the ureter and infection of the transplanted organ, also were encountered no more frequently than after the autogenous transplantation, if the same technique and caution were used. In twelve experiments in which homogenous transplantations were performed, and in which the functional efficiency of the transplant was determined by analyses of the urine and the anatomic condition of the transplant was determined by exploration, 4 cases were complicated by such postoperative sequelæ. Exploration revealed in 1 case an infarct affecting about one-sixth of the kidney, due to a thrombus in a small arterial branch; in 1 a partial occlusion of the renal vein by a thrombus on the suture line of the anastomosed vein; in 1 a kinking of the ureter due to the dislocation of the kidney in the muscle pocket, and in 1 a superficial infection of the transplant

which occurred a few days after the operation. These complications might occur with the same frequency in autogenous transplantation, in case of an accident during the operation or in the course of the postoperative treatment.

Aside from these circumstances, however, the duration, both of survival and of excretory function in the homogenous transplant, was not long. The period during which the excretion of urine from the transplant was observed in my experimentation ranged from twenty-eight to one hundred and twenty hours, an average of three days, after the transplantation. The exact length of survival was difficult to determine, but the transplant usually became necrotic or softened two or three days after the cessation of its excretory function. The remarkable fact observed in the homotransplant under such conditions was that the cessation of the excretory function of the transplant occurred in spite of the maintenance of the circulation through the organ and the establishment of free drainage through the ureter, as demonstrated by two experiments. To determine when the secretion ceased, and at the same time to obviate any possible interference of free drainage of the ureter due to occlusion of the inserted catheter, the latter was washed with sterilized physiologic salt solution or distilled water, or else the old catheter was exchanged for a new patent one. At the same time, a fairly large amount (200 or 300 cc.) of water or physiologic salt or glucose solution was given orally or intravenously, as it had been established that such solutions had a more or less diuretic effect on the kidneys of the recipient, as well as on the transplant. To ascertain whether the circulation through the transplant was being maintained an incision was made through the protruding ureter. As long as the circulation was maintained bleeding from the ureteral bloodvessels could be perceived, as the blood supply to the ureter of such a transplant came through a branch from the renal artery.

The methods just described are, to some extent, indirect, as they do not exclude such conditions as partial occlusion of the bloodvessels by thrombosis or stenosis. The catheterization of the ureter, also, may fail to sustain free drainage for a long period of time if there is kinking of the ureter. However, these methods were controlled and the real condition ascertained by subsequent exploration, the transplant being exposed in its new site and the specimen dissected for direct inspection of the anatomic condition. At this exploration any dislocation of the transplant or kinking of the ureter would have been readily seen. The maintenance of the circulation could also be ascertained by examining the pulsation of the renal bloodvessels, and the enlargement and tenseness of the kidney under compression of the vein.

Regarding infections of the transplant, a most likely occurrence in animal experimentation of this kind, the same postoperative

treatment and care were carried out as had been used in the cases of successful autogenous transplantation. In many cases of autogenous transplantation of the kidney, however, even when a superficial infection of the wound and the transplant had occurred, the kidney had continued to function in the new location if no mechanical difficulty in the blood supply or the drainage of excreted urine arose. On the other hand, in the homogenous transplantation the organ nearly always ceased to function before any apparent sign of infection of the wound or of the transplant itself appeared. With regard to this last point, I am inclined to the view that such infections were not the real cause of the cessation of function and the failure of the transplant to heal in the new location.

The function of the homotransplant followed a different course from that of the autotransplant, just as the length of functional activity and of survival varied in the two. Some similarity in function of the transplant of both kinds was observed. The beginning of the excretion of urine from the homotransplant was often perceived at the end of the operation, but the copious flow usually began a few hours later. The urine, collected and measured frequently for a certain period of time during the entire course of the experiments, showed the maximal rate of flow the first day, frequently amounting to more than 100 cc. (highest, 129 cc.) during one hour. The rate then decreased gradually or abruptly during the following days until anuria set in. The diuretic reaction of the homotransplants to the administered water, salt or glucose solution, was identical to that of the autogenous transplants. The findings coincide with those of Holloway. The concentration of the nitrogenous constituents and chlorids in the urine were low the first day, rose to the maximum the second or third day and then decreased gradually or abruptly in the same way as the quantity of urine diminished. The quantities of urine, as well as the absolute amounts and concentration of nitrogenous substances in the urine from the transplant and from the kidneys of the recipient, were greater in the latter than in the former. However, when the homotransplant was still in full activity the absolute amount, as well as the concentration of chlorids in the urine from the transplant, was larger than in the urine from the recipient's kidneys. Urine from the transplant was always alkaline in reaction at first, but later was not constant and was often acid, especially near the end of the functional activity of the organ. The chemical reaction of urine from the transplant and of that from the recipient's kidneys did not always coincide, even when the specimens were collected during the same period. Albumin in the urine from the transplant was found in most cases immediately after transplantation, then often disappeared for a time and again appeared with red blood cells, pus cells and occasional casts in the organized sediments, when the quantity of urine diminished.

Regarding the functional test on the transplant with phenolsulphonephthalein, the beginning of the excretion of this dye occurred two or three minutes after its intravenous injection. Although the output during the first hour varied according to the excretory activity of the transplant, it sometimes reached 21 per cent, and followed a course parallel to the transition of excretion of nitrogenous constituents, showing the same relation to the urine from the recipient's kidneys as previously described, except that the concentration of the dye excreted in the urine from the transplant was sometimes more pronounced than that of the recipient's bladder urine. After the subcutaneous injection of phlorizin sugar appeared in the urine from the transplant as well as in the recipient's bladder urine, but the total amount of sugar excreted by the transplant was always smaller than that by the recipient's kidneys. Lithium carmin was excreted by both the transplant and recipient's kidneys after intravenous injection.

As to the effect of the homogenous transplantation on the recipient itself, the animal showed exteriorly no marked change in its general condition, but the routine examination of the constituents of the blood before and after transplantation, as well as after removal of the transplant, disclosed some apparent change in them. The blood urea nitrogen decreased more or less (to as little as 2.95 mg. for each 100 cc.), while the transplant was functioning well and the nonprotein nitrogen and creatinin also showed some decrease at times, as had been noted by Williamson in his experiments, except that their decrease paralleled that of the urea nitrogen (Fig. 1). No marked change of the chlorids and sugar in the blood was observed. It would have been desirable also to examine the change of total excretion of nitrogenous substances from the animal for the entire course of the experiment of homogenous transplantation, but this could not be carried out under the conditions of the present experiment. However, in the functional test with phenolsulphonephthalein, which may in some measure serve this purpose, it was repeatedly observed that the amount of dye excreted during the first hour, both by the transplant and the kidneys of the recipient, was larger than that by the latter alone, while the transplant was functioning well and the urea content of blood showed the lower level. After transplantation of the kidney the neck of the animal always showed gradual swelling, coinciding with the diminution of excretion, although without any apparent sign of infection of the wound or the transplant itself. Exploration at this stage usually revealed a marked accumulation of serous bloody fluid in the muscle pocket, excessive edema of the surrounding tissues and skin and enlargement of the kidney, even when the circulation was still maintained and the drainage of the ureter free. The kidney when removed under such conditions was apparently increased in size as well as in consistency, being sometimes swollen to nearly twice its

original size. The fibrous capsule stripped easily from the surface of the parenchyma, and the surface of the parenchyma usually looked smooth, but was mottled red and gray. On section the renal tissue was very edematous and swollen, and had lost its normal transparency. The cortex had a grayish color, the medulla appeared congested and the fine renal structure in both cortex and medulla was often indistinct. The pelvis was sometimes slightly distended and its mucous membrane edematous, but usually there was no apparent sign of infection. The ureter was also swelled with edema. The anastomosed bloodvessels were patent and clean on the suture lines and free from thrombosis. However, this change of the transplant, as well as of the surrounding tissues, might vary

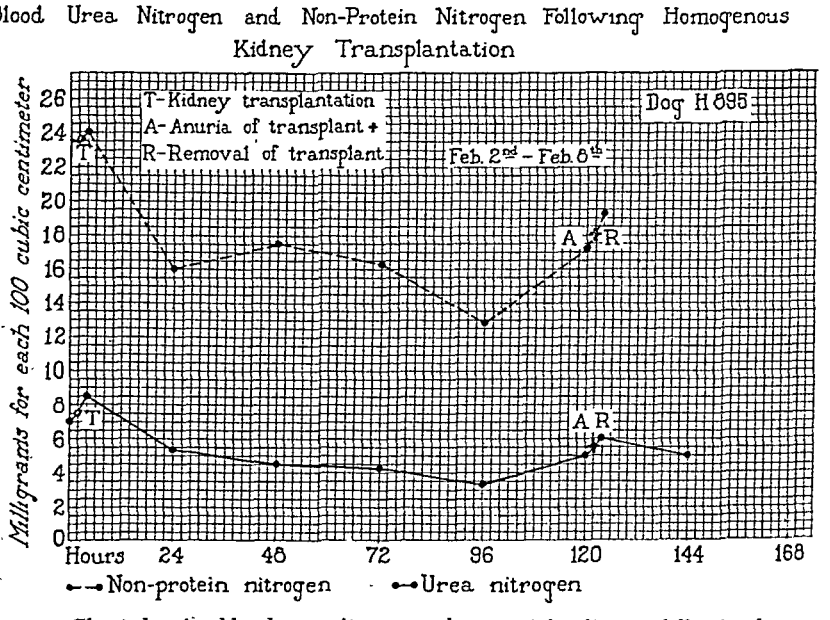


FIG. 1.—Chart showing blood urea nitrogen and nonprotein nitrogen following homogenous transplantation of the kidney.

in grade and intensity in each case and also with the different periods of time that had elapsed after transplantation. If the transplanted kidney was removed while it was still functioning fairly well it did not present such a marked picture of nephritis, but instead a cloudy swelling or degeneration of the parenchyma of varying degree. These macroscopic findings were confirmed microscopically. The kidney transplants which were removed soon after transplantation usually showed the picture of nephrosis, that is, desquamation and coarse granulation or fatty degeneration of the tubular cells, especially those of the proximal convoluted tubules and the thick limb of Henle's loop (Fig. 2). Many casts were observed in the thin limbs of Henle's loop and in the collecting



FIG. 2.—Photomicrograph of section from a homotransplanted kidney which was removed when it was actively functioning, seventy-two hours after transplantation. Marked desquamation and degeneration of tubular cells (Dog H-604) (× 120).



FIG. 3.—Photomicrograph of section from a homotransplanted kidney which was removed when it had shown marked decrease of excretion of urine, sixty-four hours after transplantation. Moderate degeneration of tubular cells, the glomeruli appearing fairly intact. Slight interstitial infiltration. (Dog H-200) (× 120).



FIG. 4.—Photomicrograph of section from a homotransplanted kidney which was removed after development of anuria, but with circulation through it intact. Specimen obtained one hundred and twenty hours after transplantation. Marked degeneration of tubules as well as of glomeruli; some casts; interstitial infiltration with leukocytes and small round cells. (Dog H-895) (× 120).

tubules, but without evidence of damage to the glomeruli (Fig. 3). However, very soon after this metamorphosis of the tubular cells infiltration of leukocytes and small round cells around glomeruli and bloodvessels in the parenchyma began, and increased gradually until the process spread throughout the interstitium of the renal tissue, but not to any marked extent in the lumen of the tubules. The glomeruli and tubules revealed at the same time progressive damage of their structure, even to fatty degeneration of glomerular tufts and necrosis of tubular cells (Fig. 4).

Discussion. This series of experiments established two facts: (1) That the period of survival of the homotransplant was short as compared with that of the autotransplant; (2) that the functional behavior of the two kinds of transplants presented certain marked differences. Whether the ultimate cause of these differences lies in the surgical and the allied mechanical factors, or in the biologic factor, must now be considered.

Observations made during this study do not support the conclusion that imperfections of surgical technique lie at the root of the differences in the length of survival and in the functional behavior of the two kinds of transplants. The same surgical technique and postoperative treatment were employed that had led to successful results in previous experiments with autogenous transplantations of the kidney into the neck of a dog. The autotransplant in this site had functioned for months in a practically normal manner, both before and after removal of the remaining normal kidney, and had maintained the animal in good health as long as the activity of the transplant had continued. But the homotransplant, although the same methods were used, failed to heal well in the new site, or to survive as long as the autotransplant. Likewise the duration of the functional activity of the homotransplant was short (a maximal of six days and an average of three) as compared with that of the autotransplant, which had continued more than ten months. The homotransplant functioned similarly to the autotransplant for a short time, but very soon failed to function as proved by chemical analysis of the urine, and functional tests on the organs, as well as by histopathologic examination of the specimens themselves. The failure of the homotransplant to heal well, to function long, or to survive for any length of time, led me to exclude the surgical and mechanical factors as the real cause of failure.

Some investigators, notably Unger, had performed homogenous transplantation in certain cases without the removal of the recipient's kidneys, and, finding disability and marked histologic (nephritic) changes in most of these transplants, had attributed them to the lack of functional demand on the homotransplants, since the physiologic function could be carried out sufficiently by the recipient's kidneys alone. I had previously ascertained that the auto-

transplant functioned well in the new location, coëxisting with the remaining kidney in the abdomen for a fairly long period (more than six months). In the present series of experiments the homogenous transplantations were also made without the removal of the recipient's kidneys, but the homotransplants were placed under such conditions that they had to function with the kidneys of the recipient. The results showed that the homotransplant, like the autotransplant, functioned with the recipient's kidneys, reducing the nitrogenous constituents of the blood, and probably eliminating more urinary constituents than were excreted by the recipient's kidneys, when the latter were in full activity. Furthermore, two other cases were observed which corroborated these results. In each of the latter one kidney from the donor was transplanted into the neck of the recipient, immediately after which, in 1 case one of the recipient's kidneys, and in the other case both, were removed. The length of survival and the functional behavior of the transplants were then ascertained by means of the collection and chemical analysis of the urine, the functional test of the kidney with phenolsulphonephthalein and the determination of the blood urea and nonprotein nitrogen. The transplants in these cases, however, showed no marked differences either in the length of survival or in functional behavior, when compared with those of the homotransplants which had been present with the recipient's own kidneys. Such considerations tend to indicate that the lack of functional demand as the cause of failure in homogenous transplantation should be excluded.

After considering the results of homogenous transplantation of all other kinds,[17, 18] which generally ended in much the same manner, the conclusion was reached that the failure of the homogenous transplantation of the kidney is chiefly due to biologic factors. Into these factors, according to many investigators,[2, 17, 19] may enter various elements, such as individual difference in cell protein, inequality of serum in osmotic relation and so forth, or such manifestations of these elements in the living organism as the toxic effect of foreign protein on the recipient, or the anaphylactic reaction of the recipient's body on the transplants.

Summary. Homogenous transplantation of the kidney was performed and studied in fourteen pairs of dogs, the same surgical technique and postoperative treatment being carried out as in the autogenous transplantation of the kidney previously studied and reported. No special consideration was given to the breed of, or relationship between, donor and recipient.

The function of the homotransplants in the neck, present with the kidneys of the recipient, was observed. This was found to continue for a few days (an average of three days) after transplantation and to end by necrosis or softening of the transplant shortly after the cessation of its function.

Chemical analysis of specimens of urine and functional tests on the transplanted kidney proved that the homotransplant functioned similarly to the autotransplant for a limited time, but the function soon changed and finally ceased, contrary to the behavior of the autotransplant, which had recovered and assumed normal function at the corresponding period when the homotransplant failed.

In the functional tests with phlorhizin, carmin and phenolsulphonephthalein the excretion of sugar and these dyes was observed in the specimens of urine from the homotransplant as well as from the recipient's kidneys. The test with phenolsulphonephthalein on the homotransplant showed that the elimination of the dye from the transplanted kidney varied according to nitrogenous constituents of urine from it, and the total amount of this dye eliminated by three kidneys during the first hour after injection was apparently greater than that eliminated by the recipient's kidneys alone before operation.

While all three kidneys were functioning the nitrogenous constituents of the blood were reduced, but the chlorids and sugar in the blood were not changed. The urea nitrogen showed the most marked reduction, but the nonprotein nitrogen and creatinin also were decreased.

The macroscopic, as well as microscopic, examination of the specimens of the homotransplant revealed that the transplanted kidneys were affected at first by nephritic changes of the parenchyma, such as cloudy swelling and degeneration of the tubular elements, and then by marked nephritic processes in the renal tissue, showing profound degeneration of glomerular and tubular elements with extensive interstitial infiltration of leukocytes and small round cells.

TABLE I.—CHEMICAL ANALYSIS OF SPECIMENS OF URINE FROM THE TRANSPLANT AND THE BLADDER OF THE RECIPIENT COLLECTED DURING THE SAME PERIOD.*

(Recipient, Dog H-200; donor, Dog G-789.)

	Volume, cc.	Color.	Reaction.	Albumin.	Total nitrogen mg.	Urea and ammonia nitrogen mg.	Ammonia nitrogen, mg.	Chlorid mg.	Phenolsulphonephthalein excretion, first hour.
Transplant	25	Clear yellow	Neutral	Positive	58.25	41.00	1.65	6.90	21 per cent in 41 cc.
Bladder	39	Clear light yellow	Slightly acid	Negative	226.20	189.90	7.80	5.77	43 per cent in 111 cc.

* Between 1.40 and 2.25 P.M. November 27, 1924.
Transplantation had been performed twenty-five hours previous to the time of securing these specimens.

This great difference in the length of survival and in the functional behavior of the homotransplant, as compared with the autotransplant, in the experimental operations which were performed in the same manner, cannot be attributed simply to the surgical or mechanical factors of the operation, but probably is due to some underlying biologic factor in homogenous transplantation, which is not as yet understood.

TABLE II.—CHEMICAL ANALYSIS OF THE BLOOD OF THE RECIPIENT FOLLOWING HOMOGENOUS TRANSPLANTATION OF THE KIDNEY.
(Recipient, Dog H-871; donor, Dog H-872.)

Date, 1925.	Time.	Mg. for each 100 cc.		Comment.
		Nonprotein N.	Urea N.	
Jan. 26	8.30 A.M.	25.0	6.6	Before operation.
	10.20 A.M.	....	....	Transplantation satisfactorily finished.
	11.50 A.M.	17.5	6.4	Secretion fairly good.
	4.50 P.M.	14.4	3.7	Secretion good, output of phenolsulphonephthalein during the first hour after injection 18 per cent in 129 cc. of urine from the transplant.
Jan. 27	8.30 A.M.	22.0	3.2	Secretion very good. Phenolsulphonephthalein, 20 per cent in 59 cc.
	11.55 A.M.	20.0	4.4	Secretion good.
	4.45 P.M.	19.5	6.45	Secretion fairly good.
Jan. 28	8.35 A.M.	12.6	4.2	Secretion decreased.
	11.30 A.M.	21.6	3.1	Secretion markedly decreased.
	4.40 P.M.	14.8	4.5	Phenolsulphonephthalein trace in 3 cc.; secretion almost ceased.
Jan. 29	8.35 A.M.	....	5.6	Anuria.
	4.50 P.M.	....	6.6	Transplant removed five hours before.

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RENAL SEPSIS ASSOCIATED WITH MANIC DEPRESSIVE INSANITY.[1]

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In view of the fact that reports of surgical procedures for the removal of foci of infection in patients suffering also from mental affections have occupied a considerable space in recent medical literature, it has seemed worth while to the writer to report the case here recorded.

The abstract of her history as received from Bloomingdale Hospital covering the period from the onset of her trouble to her discharge from that institution is as follows:

The patient, aged forty-two years, was born in the United States. Her family history is irrelevant: there is no knowledge of any nervous or psychotic disorder and her childhood and girlhood were entirely without incident connected with her present condition. After her marriage she had sufficient domestic help to relieve her of most of the usual household duties, but she had few interests and few friends. She did not dance or play cards, and, while she attended

[1] From the Roosevelt Hospital.

and enjoyed the theater, her life was otherwise pretty much of a routine of household duties, but apparently one of entire contentment to the patient. Her general health was always quite well with no ills other than a tendency to frequent attacks of flatulence.

Her menstrual history is negative. During early married life contraceptive measures were employed but later there was some desire on the part of the patient for children, and, although more recently pregnancy had not been expected she was at first alarmed and then delighted, when in 1921 it was found that she was pregnant. During the early period of the pregnancy there was slight nausea but she ate and slept well and her general health remained very good throughout her pregnancy. She was delivered of a male child in August, 1922, the delivery being instrumental but not exceedingly difficult and she afterward made an uneventful convalescence.

Her present illness became noticeable almost immediately after getting out of bed after her confinement, at which time she began to get nervous, complained of cardiac palpitation and imagined she had heart trouble.

About October 1, two months after her confinement, she complained of pains in her abdomen and across her back and at this time a diagnosis of bilary colic was made; these symptoms disappeared, however, after she had passed two small urinary calculi. By this time her nervousness had increased considerably and she complained much of cardiac palpitation and was extremely apprehensive about her heart and her health. She also had many crying spells and could not sleep without the aid of hypnotics and from this time on required the constant attention of a nurse.

It was found that she was better when she kept away from her baby, so artificial feeding was substituted for nursing and it was also noted that her condition was worse when she had visitors, she herself complaining that the latter bothered her. When her husband tried to have her do various things with the idea of promoting enjoyment for her she complained that he was trying to test her but would offer no explanation as to the nature of the testing she suspected. She had occasionally threatened suicide, stating that she was of no use in the world and only a burden to her family, and had on occasions held a knife or fork in her hand and pretended to injure herself. Principally because of these actions she was admitted to Bloomingdale Hospital on February 20, 1923, her family feeling that it was impossible to take adequate care of her at home. In the hospital the patient was frequently tearful and complained that she wanted to get out as she was worried about her baby. She admitted that she had talked of suicide, but said that she would not have done it, and she denied any real attempt at it.

While she was under observation in the hospital there was no evidence of hallucinations; no delusions could be elicited; the patient

was well oriented and without memory defects; her memory retention was good and her general intelligence was average for her social condition. Calculation was only fair, her repetition of numbers was poor, and her insight was partial. The patient stated that she felt quite upset about things not being right and admitted she was extremely nervous and apprehensive.

The general physical examination at this time showed a well-developed, fairly well-nourished woman, aged forty-two years, 5 feet 1 inch in height and weighing 119 pounds, with an essentially normal temperature, pulse and respiration.

Laboratory findings were as follows: Urinalysis was negative in the beginning, but in July there was quite a large quantity of albumin, which, however, did not persist. A Roentgen ray examination of her mouth showed badly infected teeth. The blood Wassermann was negative, and the blood cell and differential white cell counts were normal.

On June 4 she complained of pain in her left side and in her back. This was attended by a slight rise in temperature, and on June 28 this condition was repeated, the rise in temperature disappearing after colonic irritation in each instance.

On July 21, following another attack of pain, there was some tenderness and a sense of a mass in the left loin, and, on the suspicion of a kidney lesion, the phenolsulphonephthalein test was done and gave 32 per cent elimination in one hour and 47 per cent in two hours. As there was no pus in the urine at this time and a total absence of chill or fever in any attack it was presumed that there was little evidence of pyonephrosis, although it was thought that there might be a possibility of a hydronephrosis.

A Roentgen ray of the gall bladder was taken with negative results, the plate showed a rounded shadow opposite the third lumbar vertebra in the region corresponding to the pelvis of the left kidney.

On July 26, 1923, she was discharged from Bloomingdale Hospital, the discharge diagnosis being manic depressive insanity; depressive type (puerperal) and her condition noted as improved during her stay in that institution. She was admitted to Roosevelt Hospital on the following day to the writer's service. On the admission sheet the notation was made that the patient is a well-developed woman apparently not ill physically, but extremely nervous and agitated. The general physical examination elicited little of importance except that the left kidney was ptosed. The urine was turbid, contained a trace of albumin, no sugar, and the microscopic examination showed hyaline casts, calcium oxalate crystals, pus cells and red blood cells.

Blood analyses showed: Urea nitrogen, 15.9 mg.; creatinin, 1 mg.; uric acid, 5 mg.; sugar, 125 mg. per 100 cc. of plasma. The Wassermann examination was repeated and again the reaction was negative.

Cystoscopic examination showed the bladder tolerance and bladder capacity normal, although the bladder mucosa was congested and the walls trabeculated and there was much pus floating about in the distending fluid. The left ureteral orifice was distinctly congested. A catheter passed up the left ureter readily, no obstructions being noted. The flow of urine began immediately and was rapid and continuous without the intermissions normally present and the urine was turbid in appearance. One ounce of residual urine was aspirated from this pelvis, the last portion obtained being thick pus. Culture of the urine from this kidney showed a growth of Staphylococcus albus. The capacity of this pelvis for injected fluid was measured and found to be greatly increased above normal. A roentgenogram showed a shadow, evidently that of a calculus in the region of the left pelvis in close apposition to the shadow of the catheter. (Fig. 1.) A pyelogram showed a marked distention of the pelvis and calices but with a definite periphery of kidney tissue remaining, and the kidney was ptosed and rotated downward and the course of the ureter tortuous. (Fig. 2.) A catheter passed to the right pelvis readily; the flow of urine was normally intermittent in character and rapid in rate and the urine was clear. Microscopic examination of this urine was negative and cultures remained sterile at the end of forty-eight hours. Both the phlorizin and the phthalein test for kidney function were used and the former found to be positive on the right side in twenty-two minutes but still negative on the left side at the end of fifty-two minutes when the examination was terminated. While phthalein appeared in the urine from the right kidney within four minutes, and in eight minutes from the left, the reaction was noted as being strong on the right side but very faint in the urine from the left kidney.

The cystoscopic diagnosis was: A ptosed left kidney with a dilated and infected pelvis, containing a calculus; probably a pyelonephritis with very poor function of this kidney. The chemical functional tests gave good reactions in the right kidney and would indicate that this kidney was capable of performing the entire renal function.

We had here demonstrated a calculus pyelonephritis in a patient suffering also with a serious mental disturbance and one of the important aspects at this time was to evaluate the causative relationship of the former to the latter. No other gross focus of infection was apparent and while sepsis may not be generally accepted as a cause of manic depressive psychosis, it seemed reasonable to suppose that the kidney condition might be in this instance an important etiologic factor. Moreover the kidney condition in itself warranted surgical intervention.

Under ordinary circumstances, careful consideration would be given to the advisability of a pyelotomy for removal of the calculus and a nephropexy to replace the kidney in its normal condition



FIG. 1.—Roentgenogram shows ptosed kidney, calculus in pelvis and tortuous course of the ureter.

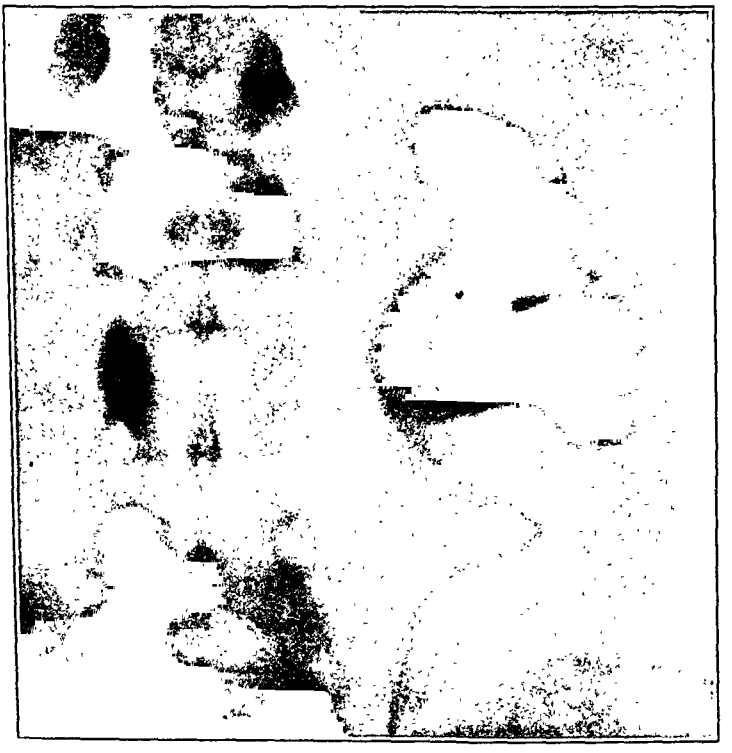


FIG. 2.—Pyelogram showing the dilated pelvis and the dilated and blunted calices.

and correct the abnormal course of the ureter as the operation of choice, with the reservation, that if unsuccessful in freeing the patient of her symptoms, a secondary nephrectomy could be done. It would seem fair to state that the chance of saving the kidney by such a conservative procedure warranted the risk of a failure under ordinary circumstances. However after considering that the other kidney showed good functional reactions to the usual chemical tests, that the blood chemistry figures were normal and that an operation affording the most rapid and uncomplicated postoperative result promised both the least strain on the patient's already badly disorganized mental state and the maximum of physical benefit, a nephrectomy was decided upon.

Operation was performed on August 1, 1923, under gas and ether anesthesia, and without undue technical difficulty I removed the left kidney and upper ureter. The kidney measured 10 cm. by 6 cm. by 4 cm. and weighed 135 gm. There was a small hematoma beneath the capsule which otherwise appeared normal and stripped readily. No abnormalities were seen on the cut surface except a moderate redness of some of the apices of the pyramids. The pelvis contained a calculus and was dilated and its mucosa showed numerous petechial hemorrhages.

Microscopic examination showed the entire wall of the pelvis to be infiltrated with round cells which were generally collected into small clumps; it was much thickened in places; parts of the epithelium were absent and the capillaries injected. As for the kidney itself, the apex of a pyramid showed dilatation of the vessels and considerable hemorrhage and edema. At the junction of calyx and pyramid there was necrosis with lymphocytic infiltration and there were also small necrotic points diffusely scattered throughout the cortex with an accumulation of lymphocytes, the latter being especially numerous just beneath the cortex. Diagnosis: pyelonephritis and renal calculus.

After a study of the sections of the kidney there is grave doubt if anything short of removal of the organ would have been successful, and, disregarding entirely the mental condition of the patient, there is no question but that the nephrectomy was the best procedure.

The postoperative course in the first three days was very stormy. Much pain was complained of and as the patient reacted very badly to the administration of morphin, attempts at relief were confined to the administration of bromids and chloral, poor substitutes for morphin for relief of postoperative pain. She slept at short intervals only, and, just as before operation, the bedside notes consisted principally of notations to the effect that the patient was restless, nervous, depressed and crying. Considerable abdominal distention was present for the first three days but this responded to the usual measures. After a few days no further concern was felt as to her physical condition, and the surgical convalescence was thereafter uneventful.

Nine days after operation a definite change for the better was noted in the patient's mental condition and that night she slept well, her first good night in many months. She was allowed out of bed on the twelfth day and was bright and cheerful all day and thereafter, and three days later she was discharged to her home. From then until the present time, a period of about two years, her mental condition has been normal and her life exactly the same as before the onset of her illness. Her physical condition has been satisfactory and no treatment has been necessary except supervision of her diet to counteract a tendency to become obese.

Discussion. Inadvisable as it undoubtedly may be to draw conclusions from one case, it does seem justifiable in this instance to infer a very definite causative relationship between the infected kidney and the disturbed mental state, particularly when the manifestations of the latter, which had persisted for nearly nine months and were of such severity as to necessitate confinement in a hospital devoted to the care of insane patients, cleared up completely and permanently within fifteen days after removal of the septic kidney.

The question of accepting the accuracy of the diagnosis of manic depressive insanity may well be raised in looking at the case in retrospect. However, it must be remembered that that diagnosis was made by competent attendants after a period of observation extending over several months.

The question of the relationship of the puerperal state might also be raised. The onset of the psychosis soon after the confinement denotes a possible, even a close connection, but the persistence of the mental condition for such a long period afterward would seem to relegate this to a position of only secondary importance and make it appear that the infection of the kidney, which had undoubtedly been present, though without symptoms, for a long period, was the active and predominating etiologic factor.

Summary. The relationship between the serious mental condition of this patient and the infection of her kidney may have been quite accidental and her return to normal mentality after operation may also have been a coincidence; still, the possibility of a direct relationship justifies the reporting of this case as one in which the kidney condition was the important etiologic factor. Furthermore the results would seem to warrant a complete and careful urologic examination in mental cases in the presence of urinary sepsis and it would seem proper to grant these patients the benefits of corrective surgical intervention.

REVIEWS.

A MEDICAL FORMULARY. By E. QUIN THORNTON, M.D., Assistant Professor of Materia Medica in the Jefferson Medical College, Philadelphia. Twelfth edition. Pp. 352. Philadelphia: Lea & Febiger, 1925. Price, $2.50.

THIS ever useful little book has become particularly desirable on account of the many changes caused by the appearance of the tenth edition of the *U. S. Pharmacopœia.* E. K.

HAND ATLAS OF CLINICAL ANATOMY. By A. C. EYCLESHYMER, B.D., PH.D., M.D., Dean of the College of Medicine and Director of the Department of Anatomy, College of Medicine, University of Illinois; and TOM JONES, B.F.A., Director of Anatomical Illustration and Instructor in Anatomy, College of Medicine, University of Illinois. Pp. 424; 395 illustrations. Philadelphia: Lea & Febiger, 1925. *Price,* $11.00.

THIS volume is an outgrowth of the work prepared for the Medical Corporation of the Army and Navy during the late war. It is divided into four parts: Part I, The Head and Neck; Part II, The Thorax, Abdomen and Pelvis; Part III, The Upper Extremity; Part IV, The Lower Extremity. The illustrations are excellent. They are arranged as: (*a*) Transparencies or projections; (*b*) systematic dissections; (*c*) regional dissections; (*d*) frontal, sagittal and transverse sections; (*e*) surgical incisions. A series of muscle projections showing the muscles in their relation to body outline and bony structures is unique and interesting. The index is good and is also explanatory which makes it doubly useful. For much of the material the authors are indebted to the authors of other well-known atlases. This book should be well received by surgeons, both special and general, as an easily available text for anatomic reference. I. R.

TRAITEMENT DU DIABÈTE. By PEDRO ESCUDERO, Professor of Clinical Medicine, University of Buenos Aires. Pp. 276. Paris: Norbert Maloine, 1925. Price, 30 francs.

A PRACTICAL satisfactory statement of the management, not merely of diabetes, but of the individual patient. The book, how-

ever, gives the impression of having been hastily put through the press, nine of the two hundred and seventy-six pages being devoted to corrections and errata in the text. The American reader will not find anything not covered at least as well in the standard American works. R. K.

BAILEY'S TEXTBOOK OF HISTOLOGY. Revised and rewritten by OLIVER S. STRONG, A.M., PH.D., Associate Professor of Neurology, College of Physicians and Surgeons, Columbia University New York; and ADOLPH ELWYN, A.M., Assistant Professor of Anatomy, College of Physicians and Surgeons, Columbia University, New York. Seventh edition. Pp. 939; 585 illustrations. New York: William Wood & Co., 1925. Price, $7.00.

IN this seventh edition the chapters on the Cell, Epithelium, Connective Tissue, Cartilage and Bone, Blood and Muscle have been rewritten and expanded by the new authors; the chapters on Nerve Tissue and the Nervous System enlarged in a capable manner and many new illustrations added. Much the largest part of the book, over four hundred pages, is devoted to the Organs (Part III), this being preceded by a short Part I on the Cell and two hundred pages on the Tissues and followed by fifty pages of Histological Technique. The illustrations, for the most part, are good, especially the photographs of the Weigert preparations, reproduced by a new method. One misses references to original papers as well as any mention of the conductive system of the heart, the different cells of the islands of Langerhans, the Kupffer cells of the liver. In fact, the important recent development of the reticulo-endothelial system seems to have escaped the reviser's attention. On the other hand, the blood, the pituitary and other ductless glands are well presented. On the whole, the book can be heartily recommended. E. K.

SYMPTOMS OF VISCERAL DISEASE. By FRANCIS M. POTTENGER, A.M., M.D., LL.D., F.A.C.P., Medical Director, Pottenger Sanitarium for Diseases of the Lungs and Throat, Monrovia, Calif. Third edition. Pp. 376; 86 text illustrations and 10 color plates. St. Louis: C. V. Mosby Company, 1925. Price, $6.50.

THE author's treatise on the anatomy, physiology and pathology of the vegetative nervous system marks a step forward in the pioneering of that region where so much is known and so little correlated. The need among the profession for enlightenment such as the author furnishes is evidenced by the fact that this is the third edition in six years.

The presentation of the subject matter is much improved. In previous editions the anatomy was treated last, but now it assumes

its rightful first place. The section is at times hard reading, but very necessary to an understanding of the regional and general vegetative functions as revealed in the rest of the book.

The conception of exophthalmic goiter as a stimulation of the vegetative nervous system by toxic thyroid products will probably meet much opposition from the New York Mt. Sinai school and their followers, who feel that thyrotoxicosis is merely a further expression of, and an individual variation from, the regular picture of autonomic imbalance.

Monographs and textbooks are notably soon out of date, but we feel that nowhere else have we seen such accurate, concise and yet complete modern information on the vegetative system gathered into one work. C. L.

EYE, EAR, NOSE AND THROAT MANUAL FOR NURSES. By ROY H. PARKINSON, M.D., Visiting Oculist and Aurist to St. Joseph's Hospital, San Francisco, Calif. Pp. 207; 51 illustrations. St. Louis: C. V. Mosby Company, 1925.

THE author has especially had in mind the student nurse when preparing this book. It is clear, simple, practical and concise. Reproductions of pen and ink drawings make a valuable contribution. The first part of the book is devoted to a discussion of the general conditions which the student nurse will meet, the second part is devoted to operating-room technic and the third part deals with the relation of the public-health nurse to this field. Pertinent information is given to her which will aid her in solving many of the problems relating to the special senses with which she is in daily contact. S. G.

CLINICAL LABORATORY MEDICINE. A Textbook of Clinical Laboratory Diagnostic and Therapeutic Procedures. By HENRY M. FEINBLATT, M.D., Director of Laboratories, United Israel-Zion Hospital; and ARNOLD H. EGGERTH, A.B., A.M., Associate Professor of Bacteriology, Long Island College Hospital, Brooklyn, N. Y. Pp. 424; 87 engravings and 2 colored plates. New York: William Wood & Co., 1925. *Price*, $5.00.

THE sections on bacteriology are very good, with the exception of the mouse method of typing pneumococci, where omission of some important details diminish the accuracy of the presentation. Cultures should be made of the heart blood and the peritoneal exudate before washing out the cavity; agglutination tests should always be made with pure cultures. The chapter on Basal Metabolic Rate is rather too much condensed for the beginner. In blood chemistry the ordinary methods are included and are more simplified and workable for the beginner than is the case in most laboratory manuals. In clinical pathology the technic given for cross-

agglutination and for blood transfusion is too brief; no mention is made of reporting hemoglobin in grams or that in testing for occult blood in feces the patient should be placed on a meat-free diet.

In general, however, the descriptions of the methods given are concise and clear, the illustrations and print splendid, the index good and the references so placed in the body of the text as to stimulate interest in the subject. For a reference book in advanced laboratory work it is not sufficiently exhaustive; but will be of value to the beginning student and the practitioner, as much weight is given to the proper significance or interpretation of laboratory findings from the clinical point of view. W. C.

MIDWIFERY MECHANICS. By LIEUT.-COL. ANDREW BUCHANAN, I.M.S. (RTD.), M.A., M.D., M.CH., M.A.O., Ex-Superintendent of Nagpur Medical School and Dufferin Hospital. Pp. 82; 12 plates. London and Shanghai: Humphrey Milford, Oxford University Press, 1924.

IN these days of mechanical obstetrics it is refreshing to note that someone is still interested in the natural physical processes concerned in parturition. This small book is an attempt to smooth out the difficulties experienced by the average student in understanding the mechanism of labor. By pictures, models, diagrams and text the "theory of the pivot points" is made clear. The large number of abbreviations and symbols is at first confusing. The book is not read with ease; it has to be studied. But a study will repay anyone interested in physics and dynamics of obstetrics. P. W.

CHRONIC INTESTINAL STASIS: A RADIOLOGIC STUDY. By ALFRED C. JORDAN, C.B.E., M.D. (CAMB.), M.R.C.P. (LOND.), Corresponding Foreign Member, Belgian Royal Academy of Medicine. Pp. 230; 315 illustrations. London: Henry Frowde and Hodder & Stoughton, 1923.

THE author has accepted in full the theories regarding intestinal stasis that have been advanced by Sir William Arbuthnot Lane and has assigned to this condition an important place in the causation of almost all bodily ills, from pyorrhea alveolaris to uterine retrodisplacement, Duputren's contraction and delusional insanity. Many statements are made with a preciseness and finality that are not justified. The book would have been more impressive if the discussion had been limited to the roentgenologic aspects of intestinal stasis. Even in this field, however, it invites criticism since many of the Roentgen-ray illustrations are only with difficulty reconciled with the legends which accompany them.

T. M.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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The Diameter of the Red Blood Cells in the Differentiation of Anemias.—About four years ago Mr. Price-Jones brought out a very interesting article followed by other articles later on a study he had made on the measurement of the red blood cells. This work had been done by several previous observers, but their technic was not as simple nor did they evolve the interesting curves which were brought out by Price-Jones. At this time the author showed that in diseases of the hematopoietic system there are interesting changes in the size of the red cells which can be accurately determined. This finding, of course, is merely an exact quantitative estimation of the well-known fact that in pernicious anemia megalocytes and megaloblasts are common. GROSH and STIFEL (*Arch. Int. Med.*, 1925, 36, 874) have simplified the technic of Price-Jones and have independently devised a method of measuring the diameter of the red cells which is a much more simple procedure than any methods as yet advocated. In a series of a considerable number of patients they found the following: The normal average diameter of the erythrocyte is 7.42 microns. In pernicious anemia the curve shows a marked tendency to be much greater, extending from 7 to 11 microns. This is a differential point in the diagnosis of this disease of value in differentiating it from malignancy, for example, in which the curves are to the left of the normal and differentiating this disease from posterior lateral sclerosis, which often resembles pernicious anemia so closely as to be thought to be the same disease.

The Value of the Icterus Index in Differentiating Anemia.—In addition to the exact measurements of the red cells which may be of importance in differentiating primary and secondary anemias, another

method has been suggested by A. V. St. George and A. Lincoln Brown (*Arch. Int. Med.*, 1925, **36**, 847) in which the information derived from a study of the icterus index is used as a basis for adding additional data to the study of a case in which differential diagnosis must be considered between primary and secondary anemia. These authors record a considerable series of cases in which they made careful studies of the blood findings with particular reference to the icterus index and they show quite definitely that the icterus index is a distinct clinical aid in separating the several types of anemias when these anemias are uncomplicated by cardiac insufficiency, biliary sepsis and pneumonia.

Efficiency of the Heart and Its Measurement.—This is the first of two lectures delivered by Dr. Yandell Henderson (*The Lancet*, 1925, **2**, 1265) at the University of London. Although this lecture was delivered primarily as a lecture in physiology, nevertheless it will repay reading by those in clinical medicine interested in cardiac physiology and the physiology of the circulation; subjects, incidentally, which should appeal to all internists and subjects in which a great deal of research work is now being conducted in this country as well as in other countries. Henderson's paper does not lend itself well to abstracting, but the conclusions that he draws from his studies are so interesting that they are well worth quoting in entirety. "The only adequate expression of the efficiency of the heart is one based on accurate measurement of the volume of blood that the heart pumps and upon the amount of oxygen consumed by the body. The relation between these two functions determines the arteriovenous oxygen difference, and thus determines the amount, and particularly the pressure of the oxygen supply to the working tissues of the body. In vigorous mammals of all sizes the arteriovenous oxygen difference during bodily rest is about 3 or 4 volumes per cent. The volume of the circulation in vigorous men and animals at rest is about 3 to 4 litres of blood per minute per square meter of skin surface. The stroke volume for animals and men of corresponding activity is a function of their body-weights not their surfaces. For all vigorous mammals, including man, the stroke index during rest is about 1.4 to 1.8 c.cm. per kilo per beat. The pulse-rate is in general proportional to the surface weight ratio and is thus in general an index of the intensity of respiratory metabolism. The mechanical conditions of the heart's activity and its own behavior make the right ventricle the meter of the circulation. The size of the stroke of this meter depends on the volume and pressure of the venous return. The veno-pressure mechanism is adjusted to act in relation to the intensity of the gaseous exchange of the tissues."

The Concentration of the Blood and the Urine in Diabetic Toxemia.—Harold A. Bulger and John P. Peters (*Arch. Int. Med.*, 1925, **36**, 857) find, in severe diabetic toxemia with marked dehydration of the blood, that the urinary chloride and nitrogen concentration is very low. Similarly the glucose content of the urine may drop as the dehydration comes on, even with a rising blood sugar concentration. There appears to be no direct relationship between the degree of dehydration and urinary changes, nor does the degree of hyperglycemia or glycosuria

seem to have any significance in these changes. The authors suggest that the kidney changes are not a result of the blood changes, but are probably brought on by the same toxic materials (ketone bodies?) acting independently on the kidneys. With insulin treatment, accompanied by glucose and saline administration, there is a rapid dilution of the blood and a rapid increase of nitrogen and chloride in the urine. They advise the giving of large amounts of glucose along with the insulin in these cases, to combat the toxic protein destruction, especially in cases with infection. Glycosuria and hyperglycosuria in themselves can be disregarded in this effort to quickly reduce the ketosis and acidosis.

SURGERY

UNDER THE CHARGE OF

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Osteitis Fibrosa and the Hyperostotic Form of Bone Syphilis.—WILHELM (*Surg., Gynec. and Obst.*, 1925, 41, 624) claims that there are gross anatomic and clinical resemblances between the hyperostotic form of syphilis of the long bones and osteitis fibrosa, both the senile hyperostotic-porotic form (Paget's disease) and the juvenile endosteal type. Coarser gross morphologic similarities, such as deformities, elongation and bowing, and especially the saber-blade form of tibia, are found in the affected bones of both diseases. Despite these external similarities, we are dealing, especially in regard to their histogenesis, with two fundamentally different diseases. The essential differences in their nature express themselves in the individual anatomicopathologic characteristics of the affected bones and also in their Roentgen pictures. Characteristic of hyperostotic syphilis are the marked, often tremendous participation of the periosteum, the more or less advanced narrowing and obliteration of the marrow cavity, the sclerotic or finely porous quality of the newly built bone tissue. The saber-blade, or saber-sheath, form of tibia in syphilis may be due purely to a periosteal new formation of bone or to an osteitic rebuilding and elongation resulting in a true bowing. Characteristic of the senile form of osteitis fibrosa are the absence of periosteal participation, the very great widening of the marrow cavity, even into the epiphyses, the frequent lengthwise splitting up of the compacta into lamellæ. The saber-blade tibia of Paget's disease is the result of rebuilding and elongation of the bone. In the juvenile endosteal hyperostotic-porotic form there is also a complete absence of periosteal involvement. The occurrence of more or less well-formed cysts or of single circumscribed dense foci accompanying a diffusely-spreading osteitic new-bone formation are disgnostic points in favor of osteitis fibrosa as against lues.

Malignant Tumors of the Kidney.—HINMAN and KUTZMAN (*Calif. and West. Med.*, 1925, 23, 429) say that the pathogenesis of kidney tumors is still in the hypothetical stage. The types most commonly found are the hypernephroma, occurring chiefly in late adult life, and embryonic mixed tumors, found in early childhood. Clinically, all renal tumors should be considered malignant, because of the great rarity of the benign type. The classic signs of kidney tumors are hematuria, pain and tumor. Hematuria is the most frequent initial symptom in adults, while tumor is in children. The importance of each symptom should be considered initially as it appears, and the diagnosis not allowed to wait until the clinical picture is complete. Only by thorough early investigation can we hope to influence the present appalling morbidity. The urologic examination should be complete, and include a differential examination of the urine functional studies and ureteropyelography.

Experimental Hydronephrosis.—HINMAN and HEPLER (*Arch. Surg.*, 1925, 2, 649) claim that it is possible to reduce urinary secretion by a properly placed, partially obstructing rubber tube on the renal artery. When this procedure, which reduces the bloodflow and the intrarenal blood pressure, is combined with total ligation of the ureter on the same side hydronephrosis develops to a much greater degree and more rapidly than when the ureter alone is ligated. This increase in the rate of development of hydronephrotic atrophy in the presence of a reduced secretory pressure and oliguria indicates that back pressure and pressure atrophy have not quite the importance generally given, but that another factor is an equally or more determining one. This other factor is a nutritional one. The more rapid parenchymal degeneration, that results from the anemia of arterial compression, weakens resistance and accelerates dilatation in spite of the diminution in back pressure.

Hepatic Function in Health and Disease.—C. H. MAYO (*Surg., Gynec. and Obstet.*, 1926, 42, 9) claims that the most common cause of death following surgical operations is disease of the lungs, the next renal complications and the third cardiac complications, although the latter condition is most feared by those who are ill. When the liver is under continued stress from congestion and the higher pressure from spasm of the sphincter of Oddi, it continues to form bile on account of the low blood pressure in liver tissue; the back pressure is not so serious nor so rapid in its results as chronic obstruction of the urinary bladder by a hypertrophied prostate. In certain cases when the liver is not functioning adequately, it may be relieved or assisted. Administering bile frees the gall bladder under tension during fasting. Its flow is increased by ox-gall and nitrogenous food, but not by calomel. Rich carbohydrate food checks it. In chronic deficiency of the liver associated with cirrhosis and splenic enlargement, the removal of the greatly enlarged spleen, reduces by 20 per cent the work of the liver and relieves and conserves the organ. In the probable deficiency consequent to chronic disease with emaciation, the lack of liver glycogen must be made up by intravenous injection of glucose.

PEDIATRICS

UNDER THE CHARGE OF

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Exanthema Subitum.—VON BOKAY (*Deutsch. med. Wchnschr.*, 1925, 51, 1687) reports the clinical findings in 11 cases of an acute illness of childhood that has been described under the name Exanthema Subitum in the American literature by Veeder and Hempelmann, Westcott, Levy and others. The disease has an acute onset, is characterized by no symptoms other than slight malaise and a fever that ranges from 102° to 104°, and after a duration of three, usually four, and occasionally five days, drops to normal by crisis. However, Glanzmann has observed a slight coryza with thin, watery nasal discharge and Levey has observed convulsions at the onset of the fever. During defervescence the rash appears; it is morbilliform, with spots ranging from 1.5 to 5 mm. in diameter, blanches on pressure, but promptly returns when the pressure is stopped. The rash appears first on the trunk where it is most abundant but rarely confluent, and may also involve the extremities and, to a less degree, the face. The rash reaches its height in twelve hours, and disappears completely in twenty-four to forty-eight hours. Desquamation has not been observed. There is a characteristic blood picture: Pronounced leukopenia (as low as 3200) with 80 to 90 per cent lymphocytes. Nine of von Bokay's cases were in infants under one year, and the oldest was two years old, but Veeder and Hempelmann met the condition in a boy of ten. The disease is apparently only very mildly contagious, having only once been observed in 2 children in the same household (Greenthal). The clinical course sharply differentiates the disease from measles and rubeola. The etiology is unknown.

The Comparative Sugar Content of the Blood and the Cerebrospinal Fluid in Various Conditions.—LEVINSON (*Am. J. Dis. Child.*, 1925, 30, 774) found that the cerebrospinal fluid sugar in his series of nonmeningitic fluids varied between 46 and 76 mg. per 100 cc. of fluid. The lowest figure was obtained in a case of brain abscess, with a turbid fluid containing many leukocytes. The next lowest figure was 50 mg. per 100 cc. The cerebrospinal fluid sugar varied from day to day, and it bore no relation to the blood sugar. The cerebrospinal fluid sugar in all forms of meningitis was low, varying from 45 mg. per 100 cc. to a mere trace. In 1 case of meningococcus meningitis, the spinal fluid sugar was unusually high a few hours after onset, but it came down to 25 mg. per 100 cc. in less than twenty-four hours. The blood sugar in these cases of meningitis varied between 84 and 176 mg. per 100 cc. The sugar in the cerebrospinal fluid in a case of encephalitis showed an insignificant rise one hour after the injection of glucose, and a rise of 8 mg. three hours after the injection of glucose. Another time it showed an increase of 4 mg. in ten and a half hours. There was a rise of from